Award Number:
W81XWH-10-1-1044

TITLE: Obesity/Overweight in Persons With Early and Chronic SCI: A Randomized, Multicenter, Controlled Lifestyle Intervention

PRINCIPAL INVESTIGATOR:
Mark S. Nash, Ph.D.

CONTRACTING ORGANIZATION:
UNIVERSITY OF MIAMI SCHOOL OF MEDICINE
Miami, FL 33136-1032

REPORT DATE:
October 2014

TYPE OF REPORT:
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PREPARED FOR:
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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6. AUTHOR(S)
Mark S. Nash, Ph.D.

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5d. PROJECT NUMBER

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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U.S. Army Medical Research and Materiel Command
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14. ABSTRACT

Overweight/obesity is pervasive after SCI and contributes to accelerated cardiovascular disease and comorbid with dyslipidemia, glucose intolerance, and insulin resistance, and is far more difficult to manage and reverse than obesity occurring in persons without disability. It is generally recommended that overweight/obese individuals lose weight by undertaking regular physically activity and consuming an energy-restricted diet to improve quality of life and reduce disease risk, although a demonstration to this effect has never been produced in persons with SCI. Here we examine the efficacy of a SCI-specific structured therapeutic lifestyle intervention (TLI) modeled after the landmark Diabetes Prevention Program (DPP) on obesity and component disease risks. The TLI consists of a 6-month clinical program incorporating 3x weekly circuit resistance training, Mediterranean-style calorie restricted diet (1200-2000 kcal/day), 16 educational sessions with a lifestyle coach, and a 6-month quasi-supervised extension (maintenance) phase. Preliminary results indicate that TLI successfully reduced body weight, improves markers of disease risk, and improves cardiopulmonary and dynamic strength fitness attributes.

15. SUBJECT TERMS
Overweight/Obesity, Spinal Cord Injury, Therapeutic Intervention

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
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Section I – Introduction

The overarching study objective is to reduce health hazards from an overweight/obese body habitus and co-morbid cardiometabolic disorders in people with SCI, and to improve their life quality. The study is a four-year multi-center randomized clinical trial (RCT) conducted at 2 SCI rehabilitation research centers and a Veterans Affairs Medical Centers. The study is modeled after the Diabetes Prevention Program (DPP), an NIH-sponsored 27-center RCT that reported a sustained 7% body weight reduction in pre-diabetic individuals accompanied by a 58% decrease in progression to type-2 diabetes. The lifestyle intervention approach incorporating diet, exercise, and behavioral adjustments was more effective than pharmacotherapy, benefited both genders and persons of all races, and has lasted 10 years after initiation.

The study plan will enroll 80 persons with SCI who are overweight/obese and have fasting atherogenic dyslipidemia and dysglycemia. Interventions will include 6 months of structured lifestyle intervention incorporating education, exercise, diet, and behavioral support. A second arm will test benefits of exercise alone while controlling for investigator contact. Multiple baselines tested before intervention will serve as a treatment control.

Exercise will include a six-month circuit resistance training program already established as effective in fitness attainment for persons with paraplegia and tetraplegia. Dietary intervention over the same period will balance caloric expenditure measured by indirect calorimetry and food intake, the latter coming from a Mediterranean style diet having effectiveness established in the DPP studies for durable weight loss and diabetes prevention. The investigators and personal 'lifestyle coaches' will then shape and follow client-specific exercise and diet programs to be conducted for 6 months in the home or community-based centers. Behavioral approaches will include a 16-week training curriculum presented in both small groups and with the lifestyle coaches. Other behavioral approaches will include customized trial information booklets performance incentives, compliance assessment, and motivational support.

Study specific aims and their accompanying hypotheses will test effects of intervention on: 1) reducing body weight and radiographically-derived body fat, 2) improving fitness as assessed by endurance, strength, and anaerobic power, 3) reducing risks of fasting dyslipidemia, post-prandial lipemia, and insulin resistance, and 4) enhancing perceived health-related quality of life. Data will be analyzed by Multivariate analysis with repeated measures. Ancillary testing will investigate effects of intervention on the whole body oxidation of fat at rest and following food intake, and examine the relationship between dietary intake and caloric expenditure at the beginning and the end of the 12 month study. The primary trial goal pays fidelity to the DPP by targeting sustained loss of 7% of body weight, a proven countermeasure for prevention of diabetes.

Section II – Body

1) IRB continuing approvals have been obtained from all study sites.

2) The study database has been approved by the Miami-VAMC and is fully operational at both the primary and secondary sites.

3) All equipment has been placed, in-serviced, and is in use for assessments. Training of research subjects is active.

4) Team meetings have been held according to schedule and the secondary site has been site visited.

5) Unanticipated numbers of screening failures in both sites are currently being tracked and have resulted in HRPO and IRB-approved protocol modifications of qualifying subject characteristics. This has increased enrollment.

We have screened and consented a total of **43** individuals for the study. After passing the initial screening, **fourteen** individuals [paraplegia (n=7) and tetraplegia (n=7)] satisfied the study inclusion criteria of obesity (BMI $\geq$ 22 kg/m^2) and fasting dyslipidemia (HDL-C $\geq$ 40 mg/dL or TG $\leq$ 150 mg/dL). Twenty-nine individuals were screened and excused [paraplegia (n=15) and tetraplegia (n=14); veteran (n=7)], in 17 cases having fasting blood glucose below the criterion score of glucose ($\geq$100 mg/dL) or lipids within a normal/healthy range (HDL-C $\leq$ 40 mg/dL or TG $\geq$ 150 mg/dL); In 1 case the subject's OGTT and HbA1c results (A1c > 10) indicated frank diabetes. The PI notified the subject of diabetic risk and he was advised to seek immediate medical intervention. In 4 cases the subjects self-reported contraindicated drug therapies; In 1 case the subject self-reported contraindicated drug therapy with previous cardiac surgery; In 2 case the subjects had been diagnosed with diabetes and had greater than 6 months of glucose lowering drug therapy; 2 Individuals had pressure sores, and 2 were non-compliant during screening.

Three paraplegia participants (Age 58 ±10.7 yrs., duration of injury 12.8±14.4 yrs.) and **2** tetraplegia participants (Age 44±3 yrs, duration of injury 16±8 yrs) have been randomized to the DPP & Exercise Group. The three paraplegic participants have completed 6-month clinical intervention and the 6-month extension phase. Results showed an **8%** average decrease in body weight and an **8%** average decrease in BMI (Table 1, Figure 1; appendix), a **3.5%** decrease in Total % Body Fat represented by **3.37%** and **17.55%** decreases in android and gynoid fat percentages, respectively. The percent change scores of the sum of all strength gains increased by nearly **17%**, with largest improvement shown in the Dip exercise (**48%**) (Table 2, Figure 2; appendix). Peak and average power increased by **9%** and **2%**, respectively. Fasting plasma glucose was decreased by **9.5%**, with an **85%** increase in insulin sensitivity (ISI) and a **35%** decrease in insulin resistance (HOMA-IR) (Table 3, Figure 3; appendix). The 2 tetraplegic participants have completed 6-month clinical intervention and just completed the 6-month extension phase testing. Preliminary results show a **4.1%** decrease in body weight and a **4.6%** average decrease in BMI. Further data analysis will be complete as this sub-group has a greater participant completion.

Two tetraplegic participants (age 52±9 yrs., duration of injury 19.5±0.5± yrs.) are randomized to the Exercise Only Group and both have completed 6-month clinical intervention and 6-month extension phase. Results to date from two participants show a **4.6%** decrease in both body weight and **4.7%** BMI. The sum of all strength gains increased by **19.6%**, with largest improvement shown in the bicep pulley-curl (**36.9%**) and the latissimus pull-down (**20%**). Power, cardiorespiratory fitness and blood results indicate minimal changes in anaerobic, aerobic fitness, Global CVD risk, insulin resistance and sensitivity.

The Shepherd Center in Atlanta has currently consented and enrolled **14** participants, and has **5** participant enrolled in the DPP & Exercise Group, and **8** participants enrolled in the 'exercise only 'group. **1** participant has withdrawn for personal reasons. **Two** participants have completed the 6-month clinical intervention and the 6-month extension phase. Assimilation of site data is currently underway.

Both testing sites are active and engaged in the research, and we successfully transitioned current subjects to the extension phase of the study, thus incorporating use of the distant care protocol. With the approval of screening criteria changes (elimination of glucose (> 100 mg/dL)) and extension phase changes (1-year to 6-months), we have been able to screen and consent a greater number of participants than in previous study years.

We have abstracted study data for presentation at the ASIA Scientific Meeting in 2013 (Chicago) and 2014 (San Antonio), including an abstract describing the behavioral component of the modified DPP program, which was nominated in the awards-eligible category.

The PI site visited the Shepherd Center in November 2013 as part of his trip to present the Apple Lecture in Atlanta, and debriefed the staff and center leadership on successes and challenges the subcontractor is experiencing.

Section III – Key Research Accomplishments

Key Research Accomplishments: Bulleted list of key research accomplishments emanating from this research.

- Completion of the population-specific:
  - Clinical Trial Manual (Appended)
  - Nutritional Manual Supplement (Appended)
  - Participant Lifestyle Manual / Lifestyle Balance Notebook (Appended)
  - Intake Form
  - Inclusion/Exclusion Check off :DOD Trial Manual (pdf): pp 5-6
  - DPP Lifestyle Materials for Sessions 1-16 (Adapted for SCI): DOD Trial Manual (pdf): pp51-156
  - Lifestyle Coach Materials: Lifestyle Coaches Manual (pdf)
  - Optional Participant Handouts: Fact Counter (pdf) / Keeping Track (pdf)

- Complete Dietary Packets for 1200, 1500, 1800, and 200 kcal
- Deployment of the study data repository and data analysis system
- Reportable Outcomes (See Section IV)

Section IV – Reportable Outcomes

Presentations incorporating information from this award:

Juried Manuscript

Nash, M.S. Physical Activity as Part of a Model Lifestyle Intervention Program for Cardiometabolic Disease***. Arch Phys Med Rehabil.*** (In Press) April, 2016.

Maher, J.L. and **M.S. Nash**. Exercise to Increase Cardiovascular Fitness in Spinal Cord Injury. ***Phys Med Rehabil*** (In Press), 2015.

Kressler J., R.E. Cowan, G.E. Bigford, and M.S. Nash. Reducing Cardiometabolic Disease in Spinal Cord Injury. **PM&R Clinics N. America** 25: 573-604, 2014.

Nash, M.S., R.E. Cowan, and J. Kressler. Evidence-based and Heuristic Approaches for Customization of Care in Cardiometabolic Syndrome after SCI. ***J Spinal Cord Med*** 35(5):278-92, 2012.

Peer-Review Abstracts

Nash, M.S., J. Kressler, P. Burns-Drecq, A. Mendez. Circuit Resistance Training improves Postprandial Glycemia but not lipid or inflammatory responses in individuals with paraplegia. ***Top Spinal Cord Inj Rehabil*** 20(1): 42, 2014.

Nash, M.S., A.J. Mendez, S.L. Groah, J. Kressler. Fasting plasma glucose values may significantly underestimate prevalence of dysfunctional glycemic regulation in persons with Spinal Cord Injury. ***Top Spinal Cord Inj Rehabil*** 20(1): 42, 2014.

Bigford, G.E., L. Brooks, P. Burns-Drecq, C. Kappy, K.Kreger, R. Munoz, D. Backus, M.S. Nash. Therapeutic Lifestyle Intervention after paraplegia significantly reduces components markers of cardiometabolic risk. ***Top Spinal Cord Inj Rehabil*** 20(1): 43, 2014.

Kressler, J., S.L. Groah, M.S. Nash. Body Mass Index is a poor indicator of body composition in persons with Spinal Cord Injury. ***Top Spinal Cord Inj Rehabil*** 20(1): 60, 2014.

Bigford, G.E., L. Brooks, P. Burns-Drecq, C. Kappy, K. Kreger, R. Munoz, D. Backus, M.S. Nash. Upper extremity cardiopulmonary endurance and dynamic strength are significantly increased in paraplegics following Therapeutic Lifestyle Intervention. ***Top Spinal Cord Inj Rehabil*** 20(1): 79, 2014.

Presentations at National/International Conference

Author and Producer: ***A Lifestyle DVD for Persons with Physical Disabilities*.** Craig H. Neilsen Foundation. (Release Date October 7, 2014, ACRM Annual Conference, Toronto, Canada).

Wellness After SCI: Are We Barking Up The Wrong Tree? ***[Featured Luncheon Speaker]*** SCI-Special Interest Group Luncheon. 91st Annual Conference of the American Congress of Rehabilitation Medicine, Toronto Canada, October 2014.

Fitness and Physical Capacity after SCI: A Marriage Made in Heaven? [Keynote] International Spinal Cord Society Annual Scientific Meeting, Maastricht, The Netherlands, September 2014.

Cardiometabolic Disease after Spinal Cord Injury: Guideline-Driven Approaches to Patient and Health Management. [Plenary Lecture] International Collaboration on Repair Discoveries (ICORD) 2014 Trainee Symposium, Vancouver, British Columbia, June, 2014.

Health and Well-Being Throughout Life With SCI [Keynote]. International Spinal Cord Injury Conference: Toward Better Quality Of Life. Sultan Bin Abdulaziz Humanitarian City, Riyadh KSA, March 2014.

Cardiometabolic Component Hazards Accompanying Spinal Cord Injury: Guideline-Driven Approaches for Effective Risk Management. Medical University of South Carolina, Webinar for the NIDRR RRTC on Aging with SCI. Charleston, SC, October, 2013.

Cardiometabolic Disease Risk after Spinal Cord Injury: Guideline-Driven Management Approaches. *28ème* Congrès *de la Société Française de Médecine Physique et de Réadaptation (*SOFMER*), Reims, France, October, 2013.*

Intensive Lifestyle Intervention after Paraplegia Significantly Reduces Cardiometabolic Risks: A Two-Subject Case Report. [Poster] Annual Meeting of the American Spinal Injury Association, Chicago, IL, May, 2013.

A Population-Relevant Lifestyle-Intensive Intervention for Diabetes Prevention after SCI. American Spinal Injury Association (ASIA) Annual Scientific Meeting, Chicago, IL, USA, May 2013.

Spinal Cord Injury: Evidence-based and Heuristic Approaches to Customization of Care for Cardiometabolic Syndrome [Keynote]. 5th Canadian National Spinal Cord Injury Conference: Translating Neural Engineering and Novel Therapies, Toronto, Canada, September 2012.

Section V – Conclusion

Trial preparation as outlined in the scope of work has been completed and work initiated within the past year. Continuing reports to local ethical authorities have been approved at all sites. All equipment and study manuals are in current use. No adverse events or serious adverse events have been experienced. Subjects have been recruited, qualified, and are currently undergoing described interventions; subjects have now entered the maintenance phase of intervention. Outcome data were sufficient to justify presentation at the national meeting of the American Spinal Injury Association, and to earn designation by the Research Committee as "award eligible" for the conference in 2013.

Benefits of the intervention in the form of significant weight loss and improved health are apparent, consistent with hypothesized benefits, and self-reinforcing among the study subjects. A site visit to the subcontractor confirms their consistency with the protocol administration at the primary research center. While study accruals have been slow, we have identified the primary reason for screening failures and taken corrective actions without undertaking additional protocol changes. There have been no screening issues since protocol amendments were approved.

Section VI – Appendices

A. Data Tables and Figures
B. DSMB Chair Letter
C. IRB Continuing Approvals (UM/MSOM, Miami-VAMC, and Shepherd Center)
D. ASIA Abstracts
E. Juried Manuscript

	Body Mass (kg)					BMI (kg/m2)				
	Baseline	6 Months	% Change BL	12 Months	% Change BL	Baseline	6 Months	% Change BL	12 Months	% Change BL
Subject1	81.90	76.80		75.70		28.86	26.51		26.13	
Subect2	157.70	139.50		137.70		43.97	40.76		40.23	
Subject3	79.50	79.80		79.50		29.58	27.61		27.51	
Group Mean	**106.37**	**98.70**	-7.2077719	**97.63**	-8.2105923	**34.14**	**31.63**	-7.3559016	**31.29**	-8.2401811

Table 1

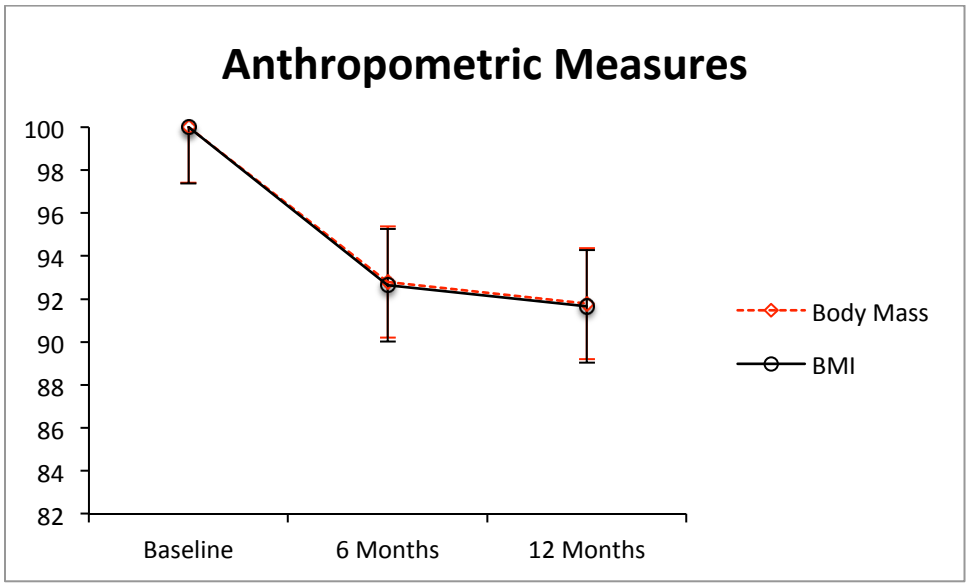

Figure 1

Isoinertial Capacity (1RM SUM)					Isoinertial Capacity (1RM DIP)				
Baseline	6 Months	% Change BL	12 Months	% Change BL	Baseline	6 Months	% Change BL	12 Months	% Change BL
363.83	420.00		396.50		54.49	69.00		64.00	
396.45	507.00		476.60		48.06	92.00		87.20	
357.20	455.00		442.00		48.06	69.00		72.00	
372.49	**460.67**	23.6708454	**438.37**	17.6841742	**50.20**	**76.67**	52.7212549	**74.40**	48.2060178

Table 2

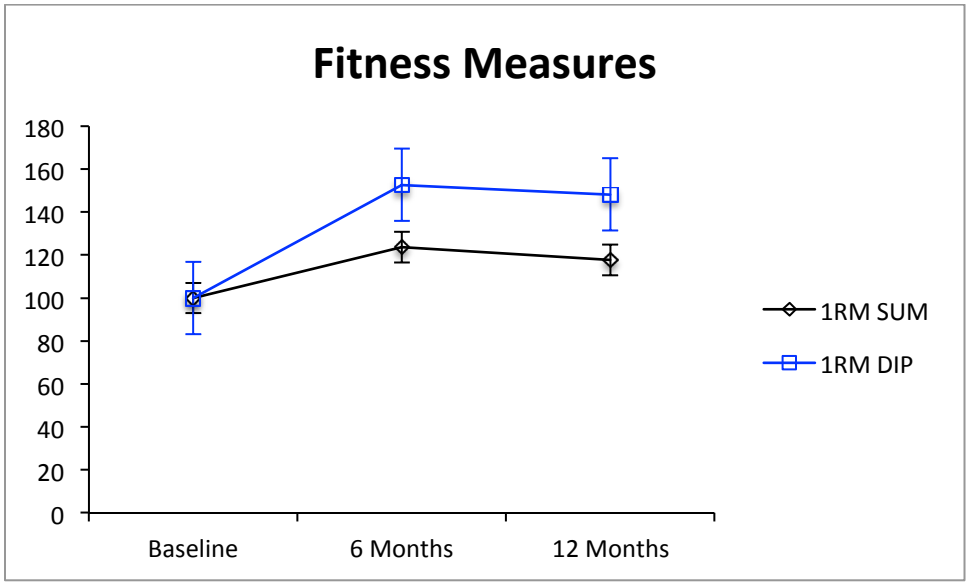

Figure 2

	Fasting Glucose					ISI					HOMA-IR				
	Baseline	6 Months	% Change BL	12 Months	% Change BL	Baseline	6 Months	% Change BL	12 Months	% Change BL	Baseline	6 Months	% Change BL	12 Months	% Change BL
Subject1	138.00	123.00		114.00		1.64	3.26		3.04		3.42	2.97		2.49	
Subject2	105.00	95.00		89.00		1.87	3.73		6.78		6.03	3.42		1.91	
Subject3	108.00	85.00		114.00		2.78	3.26		1.81		4.34	2.17		4.52	
Group Mean	**117.00**	**101.00**	-13.675214	**105.67**	-9.6866097	**2.10**	**3.42**	62.9240477	**3.88**	84.8591878	**4.60**	**2.85**	-37.943923	**2.97**	-35.334088

Table 3

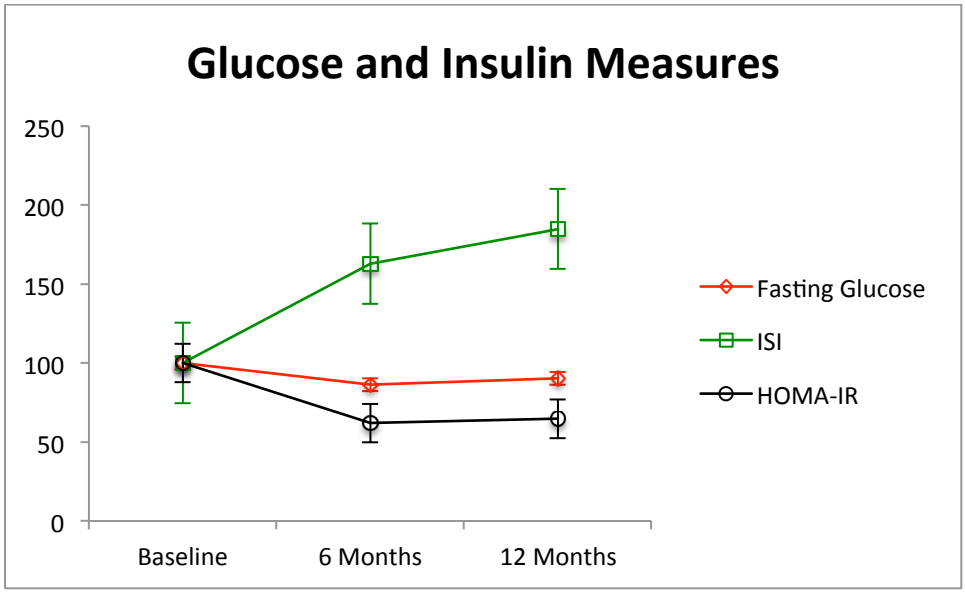

Figure 3

DEPARTMENT OF VETERANS AFFAIRS
VA BOSTON HEALTHCARE SYSTEM
1400 VFW Parkway SCI (128)
West Roxbury, MA 02132

In Reply Refer To:

May 21, 2014

Mark S. Nash, Ph.D., FACSM
Department of Neurological Surgery
The Miami Project to Cure Paralysis
University of Miami Miller School of Medicine
Lois Pope Life Center
1095 NW 14th Terrace, R-48
Miami, FL 33136

Re: SC090095 or W81XWH-10-1-1044, Obesity/Overweight in Persons with Early and Chronic SCI: A Randomized Multi-Center Controlled Lifestyle Intervention

Dear Dr. Nash:

As DSMB Chair for the above-captioned award I have reviewed the latest sponsor report and IRB approvals forwarded to my attention. I am aware that an amendment to the screening procedures has been implemented that modified elevated fasting glucose as an inclusion criterion and shortened the extension phase of the intervention. Otherwise, outcomes reported at the recent Annual Conference of the American Spinal Injury Association (ASIA) are consistent with those hypothesized in the original proposal and there have been no adverse events reported to the IRBs at any of the study sites.

Based upon my review, I authorize you and your colleagues to continue with the trial, and ask you to keep me advised of any amendments approved by your Science Officer and HRPO, as well as information concerning (serious) adverse events.

Sincerely,

Sunil Sabharwal, M.D.
Chief, SCI Service (128), VA Boston HCS
Assistant Professor of Physical Medicine and Rehabilitation
Harvard Medical School

cc: Jonathon Myers, Ph.D.
Randall Keyser, Ph.D.

UNIVERSITY
OF MIAMI

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Fax: 305-243-3328
www.hsro.miami.edu

APPROVAL

July 9, 2014

Mark Nash
305-243-3628
msnash@miami.edu

Dear Dr. Mark Nash:

On 6/5/2014, the IRB reviewed the following submission:

Type of Review:	Continuing Review
Title of Study:	Obesity/Overweight in Persons with Early and Chronic SCI: A Randomized MultiCenter Controlled Lifestyle Intervention
Investigator:	Mark Nash
IRB ID:	CR00000801
Funding:	None
IND, IDE, or HDE:	None
Documents Reviewed:	• 20100464_ICF_IRBApp06172013_UMMain_ENG.pdf, Category: Consent Form; • ASIA 2013 DOD - CASE SERIES 111412.docx • ASIA 2014 DOD - CASE SERIES CMS_PPL 31oct2013.pdf • ASIA 2014 DOD - CASE SERIES Fitness 31oct2013.pdf • Letter Nash DSMB 5-13.pdf • Report to DOD 2013.pdf • Velos Participant Data.docx

The IRB approved the study from 6/5/2014 to 6/4/2015 inclusive. Before 6/4/2015 or within 45 days of the approval end date, whichever is earlier, you are to submit a completed Continuing Review to request continuing approval or closure.

If continuing review approval is not granted before the expiration date of 6/4/2015 approval of this study expires on that date.

NOTE: Translations of IRB approved study documents, including informed consent documents, into languages other than English must be submitted to HSRO for approval prior to use.

In conducting this study, you are required to follow the requirements listed in the Investigator Manual (HRP-103), which can be found by navigating to the IRB Library within the IRB system

Should you have any questions, please contact: Joseph Datko, IRB Specialist, (phone: 305-243-1848; email: jad123@med.miami.edu)

Sincerely,

[This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature]

Amanda Coltes-Rojas, MPH, CIP
Director
Regulatory Affairs & Educational Initiatives

Department of Veterans Affairs

Memorandum

Date: November 7, 2014

From: Associate Chief of Staff for Research and Development (151/546)

Subj: Acknowledgment of Continuing Review for Protocol 5981.02

To: Mark Nash, Ph.D.

1. The Associate Chief of Staff for Research has reviewed and concurs with the Human Studies Subcommittee decision regarding approval or termination of the study entitled "EObesity/Overweight in Persons with Early and Chronic SCI".

2. If you have any questions, please contact the ACOS for Research at 305-575-3179.

Robert M. Jackson, M.D.

Human Studies Subcommittee (IRB)
Miami VA Healthcare System
1201 Northwest 16th St. • Miami, FL 33125-1693 • 305-575-3179 • Fax: 305-575-3126

IRB APPROVAL - Continuing Review

Date: November 7, 2014
From: Leonardo Tamariz, MD, MPH, Chairperson
Investigator: Mark Nash, Ph.D.
Protocol: Obesity/Overweight in Persons with Early and Chronic SCI
ID: 00889 Prom#: 0002 Protocol#: 5981.02

The following items were reviewed and approved at the 11/06/2014 meeting:

- Tracking Log for Reportable and Non-Reportable Eve - Tracking Log (10/30/2014; Continuing Review 2014)

The PI has submitted the Tracking Log for Reportable and Non-Reportable Events for the above protocol.

- Disclosure of Financial Interests - COI_A. Martinez-Arizala (11/06/2014; Continuing Review 2014)

Annual Review for Financial and/or Non-Financial Disclosure.

- Disclosure of Financial Interests - COI_M. Nash (10/30/2014; Continuing Review 2014)

Annual Review for Financial and/or Non-Financial Disclosure.

- Consent Form - Main Study Informed Consent (11/06/2014; Continuing Review 2014)
- Consent Form - Main Study Informed Consent (02/12/2014; Amendment 13/302)
- Report of Team Members - Appendix F (10/30/2014; Continuing Review 2014)

The following personnel are listed on the Report of Research Staff Members form: M. Nash and A. Martinez-Arizala.

- Proof of Human Studies Training - Completion of CITI/GCP Training (10/31/2014; Continuing Review 2014)

All personnel listed on the Report of Research Staff Members form have completed the CITI/GCP web based human studies training.

- Continuing Review/Termination Form - Continuing Review (10/30/2014; Continuing Review 2014)

Study is open to enrollment and no subjects have been enrolled to date.

- Universtiy of Miami CR Approval (07/09/2014; Continuing Review 2014)

The PI has submitted the continuing review approval letter from the Universtiy of Miami for the above protocol.

- Protocol History - Protocol History (10/31/2014; Continuing Review 2014)

This report provides a detail activity history of the above mentioned protocol.

- HIPAA Authorization Document - HIPAA Authorization/Revocation Form (11/06/2014; Continuing Review 2014)

REVISED - New Form

- HIPAA Authorization Document (12/06/2012; Continuing Review 2012)

Approval is granted for a period of 12 months and will expire on 11/05/2015. Your Continuing Review

is scheduled for 09/03/2015.

Approval by each of the following is required prior to study continuation (unless Exempt):
Human Studies Subcommittee (IRB)
Research & Development Committee

Approval for study continuation is contingent upon your compliance with the requirements of the Research Service for the conduct of studies involving human subjects.

Shepherd Center
2020 Peachtree Road, NW Atlanta, GA 30309-1465 404-352-2020 shepherd.org

Project #: 525
Event #: 183475-23

DATE: September 4, 2014

TO: *Elizabeth Gonzalez, RC, HCI*

FROM: Jeffrey A. Lewis, Manager
Shepherd Center Research Review Committee

RE: Project # 525 - [183475-23] Obesity/Overweight in Persons with Early and Chronic SCI: A Randomized Multi-Center Controlled Lifestyle Intervention

Request for Project Continuation Approval with submission of Annual Status Report on behalf of Deborah Backus, PT, PhD

On behalf of the Shepherd Center Research Review Committee, this is to acknowledge receipt of a copy of your Annual Status Report dated September 3, 2014, submitted under cover of your letter dated September 3, 2014, which has been reviewed and approved, extending approval for the project through September 9, 2015.

Enclosed is the dated/stamped Informed Consent Form, approved for one additional year until September 9, 2015, which must be used for enrolling subjects into this protocol. One month before expiration you will be reminded to inform the RRC of the status of this project. Re-approval must be granted before the expiration date or the project will automatically be "suspended".

Failure to receive a notification that it is time to renew does not relieve you of your responsibility to provide the RRC with a request for "Continuation Approval" in time for the request to be processed and approved before your expiration date.

Changes in the research may not be initiated without RRC review and approval except where necessary to eliminate hazards to human subjects. Any changes, which have been necessary for the above reasons, must be promptly reported to the RRC.

The Principal Investigator must report to this office, in writing, within 10 days, any unanticipated problems involving risks to the subjects or others. Records pertaining to research must be retained for at least three years after completion of the research.

Sincerely,

Jeff Lewis, IRB Manager

Circuit Resistance Training Improves Postprandial Glycemic but not Lipid or Inflammatory Responses in Individuals with Paraplegia

Mark S. Nash, Ph.D.[1,4,5]; Jochen Kressler,Ph.D.[1]; Patricia Burns-Drecq, M.D.[1]; Armando J. Mendez,Ph.D.[2,3]

[1]The Miami Project to Cure Paralysis; [2]Department of Medicine; [3]Diabetes Research Institute, [4]Department of Neurological Surgery; and [5]Department of Rehabilitation Medicine
Miller School of Medicine; University of Miami, Miami, Florida USA

Objective: To examine responses to 6 months of circuit resistance training (CRT) on fasting and postprandial (PP) blood glucose (BG) and insulin, the homeostasis model assessment (HOMA) for insulin resistance (IR), and lipid profile and inflammatory markers. To assess differences between chronic and training effects and effects of a recent bout of exercise, PP maneuvers were undertaken 48-72 h (chronic) or (on a separate occasion) 13-16 h (sub-acute) following exercise.

Design/Methods: Longitudinal training study with wash-in control. 14 persons with chronic (≥ 1 year) paraplegia (T4-L1, AIS A-C) underwent 6 months of CRT performed 3x/wk. Blood samples were obtained every 3 months following an overnight fast, and thereafter during an 8-hour prandial challenge using fast food feeding at 0 and 4 hours.

Results: Improvements in cardiovascular endurance (as VO_{2PEAK}) were observed from baseline to 6 months (22.4±27.0%, p=.008) but no effects on blood lipids or inflammatory markers accompanied these changes. However, after 6 months of CRT the peak PP BG response was significantly reduced by 26±39 mg/dL, p=.029. This benefit was accompanied by lowering of the peak PP insulin (-0.15±0.41Ln(IU), p = .194) and explained by significant training-induced improvement in the HOMA-IR (-0.37±0.56 Ln(mg*IU/dL), p = .028). No consistent differences were observed for chronic vs. sub-acute training effects.

Conclusion: 6 months of CRT is effective for improving PP glycemic responses in persons with chronic paraplegia - including reduced insulin resistance - yet did not significantly affect lipid profiles or inflammatory responses. Lipid and inflammatory biomarkers were significantly out of reference range, which may have influenced these outcomes. Absence of differences between sub-acute and chronic post-exercise benefits in PP responses suggests that carryover effects of exercise on glycemia may be shorter than observed in persons without disability.

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Fasting Plasma Glucose Values May Significantly Underestimate Prevalence of Dysfunctional Glycemic Regulation in Persons With Spinal Cord Injury.

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Objective: Studies in non-disabled persons have reported poor agreement between fasting plasma glucose (F-PG) and routine clinical challenge tests. As the prevalence of type-2 diabetes mellitus in the spinal cord injured (SCI) population is 20%, and impaired glucose tolerance as high as 34%, this discrepancy might significantly impact cardioendocrine disease diagnosis and future risk assessment. Thus, the current study compared agreement in identifying conditions of euglycemia, pre-diabetes, and diabetes in persons with chronic SCI based upon FPG, oral glucose tolerance testing (OGTT), and various prandial challenges (PC).

Design: Retrospective analysis of seven cross-sectional studies.

Participants/Methods: Blood samples from 187 subjects were analyzed for F-PG (after an overnight fast), 2-hour PG following a standard 75g glucose challenge OGTT (*n*=142), and maximal PG (PG_{max}) spanning a 4-hour period following various mixed-composition prandial challenges (*n*=45). Responses were categorized according to American Diabetes Association guidelines as euglycemic (F-PG<100mg/dL, post-challenge (PC) PG< 140mg/dL), pre-diabetic (F-PG =100-125 mg/dL, PC-PG =140-199 mg/dL) and diabetic (F-PG ≥126 mg/dL, PC-PG≥ 200mg/dL). Discordance of diagnosis based on these categories was analyzed with the McNemar Test.

Results: Only 10% of subjects were identified as having impaired glucose control (IGC) based on F-PG, while 2-hour PC-PG identified a total of 22%. For the subsample with PGmax values IGC was identified in 60% of subjects.

	Pre Diabetic			Diabetic		
	Number	%	*p* vs. FPG	Number	%	*p* vs. FPG
FPG	16	9	-	2	1	-
2h PCPG	35	19	.004	6	3	.125
PG_{max}	21	38	.015	12	22	.002

Conclusion: F-PG testing significantly underestimated the number of people with SCI having dysfunctional glycemic control when compared to OGTT and PC-PG. This difference may

substantially impact diagnosis, treatment, and future cardioendocrine disease risk, and thus warrants clinical attention.

Support: NIDRR RRTC on Secondary Conditions in the Rehabilitation of Individuals with SCI #H133B090002.

Therapeutic Lifestyle Intervention After Paraplegia Significantly Reduces Component Markers of Cardiometabolic Risk

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Objective: The landmark Diabetes Prevention Program (DPP) reported that body mass (BM) reduction of ≥7% through therapeutic lifestyle intervention (LI) delayed diabetes onset. We have adapted the LI for persons with spinal cord injury (SCI). This study reports the effects of the clinical LI program and ensuing maintenance phase on component risks for cardiometabolic syndrome (CMS).

Design: Intervention with repeated assessments.

Participants/Methods: Adult ♂, n=3: Age 48.9 ± 7.2; Duration of injury 12.8 ±14.4; Level of injury T3-T7; AIS A; Obese; pre-diabetic/insulin resistant, underwent a 6-month LI program incorporating 3x weekly circuit resistance training, Mediterranean-style calorie restricted diet (1200-2000 kcal/day), 16 educational sessions with a lifestyle coach, and a 6-month quasi-supervised extension (maintenance) phase (MP).

Results: Group mean BM decreased 7.2% and 8.2% from baseline after LI and MP, respectively. Fasting glucose decreased 13.7% and 9.7% from baseline after LI and MP, and insulin resistance (as HOMA-IR) was reduced from 4.3% at baseline to 2.2% after LI but increased to 4.52% after MP. Postprandial glycemic control (as AUC) improved 16.2% and 11.4% from baseline after LI and MP. Total Fasting cholesterol (TC) was unchanged after LI, but reduced 8.3% from baseline after MP, HDL-C increased 12.0% and 4.3% from baseline after LI and MP, and global CVD risk (as TC:HDL) was lowered 12.1% and 14.9% from baseline after LI and MP.

Conclusions: Success was achieved in reducing the DPP BM criterion for diabetes prevention by ≥7%, accompanied by improved fasting and postprandial glucose levels, insulin sensitivity, and lipid-related CMS risks after LI. Although recidivism was apparent after MP, results remained improved from baseline, and at 'low CMS risk' according to ADA/AHA guidelines. Continually developed strategies to improve durability, and larger sampling are needed to affirm long-term compliance and success.

Support: Funded by the U.S. Department of Defense grant #SC090095 (W81XWH-10-1-1044).

Body Mass Index is a Poor Indicator of Body Composition in Persons With Spinal Cord Injury.

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Objective: Body mass index (BMI) is routinely used as an expedient proxy for body mass and cardioendocrine disease risk. This study assessed the associations of BMI and indices of radiographically-derived body composition in men and women with chronic spinal cord injuries (SCI).

Design: Cross-sectional study.

Participants/Methods: 67 men and 11 women (19-38 years of age, 23% White (W), 37% African American (AA), 40% Hispanic (H)) with chronic (≥ 1 year) SCI (C-L1) were measured for body mass on a calibrated scale. Height was self-reported. Body composition was assessed by dual x-ray absorptiometry to discriminate whole body fat percentage (WBF%), total tissue weight, fat weight, and trunk tissue and fat weights.

Results: BMI was generally not highly correlated with any aspect of body composition (r=.054-.836, p ≤.001-.639). Particularly striking was the poor association (R^2= .454, p < .001) of BMI and WBF%, indicating that less than half of the variability in WBF% is associated with BMI. This finding was largely independent on the level of BMI (interaction Δr^2=.042, p=.015). Women had a lower association than men (R^2= .393, p < .039 and R^2= .464, p < .001, respectively) but the difference was not statistically significant (p=.803). The association between BMI and WBF% was weakest for W (R^2= .252, p < .034) compared to AA (R^2= .569, p < .001) and H (R^2= .535, p < .001), however these differences were not statistically significant (p=.184-.238 for comparison vs. W). Higher associations were seen for several measures of total tissue weight and fat weight (R^2=.469-.602, p <.001), the highest being trunk tissue weight (R^2=.699, p <.001) and trunk fat weight (R^2=.658, p <.001).

Conclusion: BMI is not a legitimate surrogate for whole body composition in persons with SCI.

Support: NIDRR RRTC on Secondary Conditions in the Rehabilitation of Individuals with SCI #H133B090002.

Upper Extremity Cardiopulmonary Endurance and Dynamic Strength are Significantly Increased in Paraglegics Following Therapeutic Lifestyle Intervention.

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Objective: The spinal cord injury (SCI) population occupies the lowest end of the human fitness spectrum, sometimes lacking the necessary fitness to perform essential daily activities. Several lifestyle hazards including physical inactivity, hyper-caloric/fat diet, and poor behavioral support contribute to this observation. This study examined effects of therapeutic LI adapted from the Diabetes Prevention Program (DPP) on upper extremity cardiopulmonary endurance and dynamic strength in persons with chronic SCI.

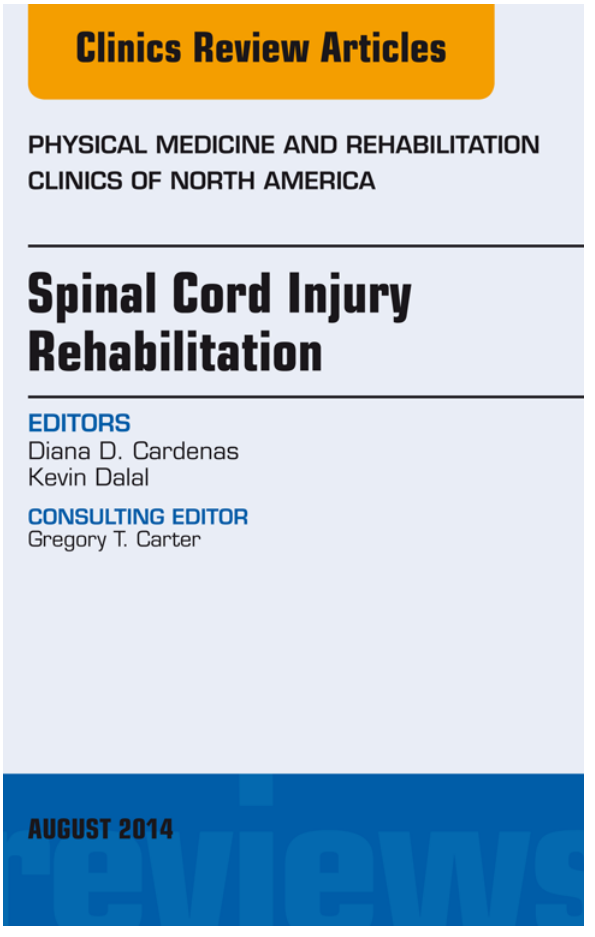
Design: Intervention with repeated assessments.

Participants/Methods: Adult ♂, n=3: Age 48.9 ± 7.2 years; Duration of injury 12.8 ±14.4 years; Level of injury T3-T7; AIS A; Obese; pre-diabetic/insulin resistant, underwent a 6-month LI program incorporating 3x weekly circuit resistance training, Mediterranean-style calorie restricted diet (1200-2000 kcal/day), 16 educational sessions with a lifestyle coach, and a 6-month quasi-supervised extension (maintenance) phase (MP).

Results: Group mean cardiopulmonary endurance (as VO_{2PEAK}) was increased by 38% and 23.6% from baseline after LI and MP, respectively. The sum of upper extremity dynamic strength (as 1-repetition maximum (1RM) sum) was increased by 23.7% and 17.6% from baseline after LI and MP, with the greatest strength increase from baseline observed in the dip exercise (1RM dip) at 52.7% and 48.2% after LI and MP.

Conclusions: Population-specific LI was successful in increasing cardiopulmonary fitness and upper extremity dynamic strength. These fitness attributes are essential in effectively performing activities of daily living and improving health parameters. Minor, yet evident decay in fitness attributes follows the supervised clinical phase, but remained improved from baseline values. Effectively developing maintenance strategies for physical activity and larger sampling and follow-up testing for durability are needed to affirm program success.

Support: Funded by U.S. Department of Defense grant #SC090095 (W81XWH-10-1-1044).



Reducing Cardiometabolic Disease in Spinal Cord Injury

Jochen Kressler, PhD[a,b], Rachel E. Cowan, PhD[a,b], Gregory E. Bigford, PhD[a,b], Mark S. Nash, PhD[a,b,c,*]

KEYWORDS

• Diet • Exercise • Behavioral modification • Drug therapy
• Cardiometabolic syndrome • Spinal cord injuries

KEY POINTS

- Accelerated cardiometabolic disease is a serious health hazard after spinal cord injuries (SCI).
- Lifestyle intervention with diet and exercise remains the cornerstone of effective cardiometabolic syndrome (CMS) treatment.
- Behavioral approaches enhance compliance and benefits derived from both diet and exercise interventions and are necessary to assure that persons with SCI profit from intervention.
- Multitherapy strategies will likely be needed to control challenging component risks, such as gain in body mass, which has far reaching implications for maintenance of daily function as well as health.
- In cases where lifestyle approaches prove inadequate for risk management, pharmacologic control is now available through a population-tested monotherapy.
- Use of these clinical pathways will foster a more effective health-centered culture for stakeholders with SCI and their health care professionals.

CARDIOMETABOLIC RISKS IN SCI

Health hazards posed by all-cause cardiovascular disease (CVD) and co-morbid endocrine disorders are widely reported in persons with spinal cord injuries (SCI).[1–3] The contemporary descriptor cardiometabolic syndrome (CMS) represents a complex

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array of these hazards, which by evidence-based clinical diagnosis encompasses 5 component risks of central obesity, hypertriglyceridemia, low-plasma high-density lipoprotein cholesterol (HDL-C), hypertension, and fasting hyperglycemia (**Table 1**).[4–7] Left untreated, these risks promote atherosclerotic plaque formation and premature CVD, and when identified in clusters of 3 or more risks, confer the same clinical threat as frank diabetes or extant coronary artery disease.[6]

Special Concerns for Persons with SCI (Accelerated Risk and Specific Targets)

Convincing evidence supports the population-specific threat to persons with SCI for an accelerated trajectory of CMS, which is typically seen as component risks of central obesity,[8,9] impaired fasting glucose and frank diabetes,[10,11] dyslipidemia,[1,12] and (depending on the nature and level of injury) hypertension. Blood pressure, however, is a 2-sided issue in the SCI population. Persons with high-level SCI (T6 or above, where sympathetic nervous system control is likely compromised[13,14]) frequently suffer from hypotension.[15] Persons with lower-level injuries have similar hypertension issues as the general population.[16] Target levels for markers of these CMS risks have been established (see **Table 1**) for the general population but not specifically for SCI. In the absence of specific recommendations, general targets for lipid and glycemic markers may be adequate for persons with SCI. However, standard categories for common surrogate measures of obesity, such as waist circumference (WC) or body mass index (BMI), are not applicable for SCI and should be adjusted to greater than 94 cm WC[17] and $\geq$22 kg/m^2 BMI,[18] respectively.

THERAPEUTIC LIFESTYLE INTERVENTION

Guideline-driven interventions to reduce CMS risks follow a pathway that first eliminates drugs and biologic agents that might be causing the CMS, which would include tobacco use. Otherwise, little in the pharmacopeia of persons with SCI would cause or

Table 1
Cardiometabolic component risks

	Criterion	
Risk	**ATP III**	**WHO**
(Abdominal) obesity	• WC >40 inches (102 cm) for men • WC >35 inches (88 cm) for women • WC >37 inches (94 cm) for persons with SCI[a]	• WHR >0.90 for men • WHR >0.85 for women • BMI $\geq$30 kg/m^2 for men and women • BMI $\geq$22 kg/m^2 persons with SCI[a]
Triglycerides	• $\geq$150 mg/dL (1.7 mmol/L)	
HDL-cholesterol	• <40 mg/dL (1.03 mmol/L) for men • <50 mg/dL (1.29 mmol/L) for women	• <0.9 mmol/L for men • <1.0 mmol/L for women
Blood pressure	• $\geq$130/85 mm Hg, or use of medication for hypertension	• 160/90 mm Hg
Hyperglycemia	• FPG $\geq$100 mg/dL (5.6 mmol/L), or use of medication for hyperglycemia	• DM/IGT/IFG
Microalbuminuria	• N/A	• $\geq$20 μg/min, or albumin:creatinine ratio $\geq$20 mg/g

[a] Adjusted for SCI based on Refs.[17,18]

worsen the CMS. Thereafter, comprehensive therapeutic lifestyle intervention (TLI) focusing on changes of dietary, exercise, and behavioral components is instituted. If these measures fail to correct the hazard, pharmacotherapy becomes the default intervention. This article provides details for each of these risk countermeasures. A clinical pathway outlining the treatment decision-making in this respect is shown in Fig. 1.

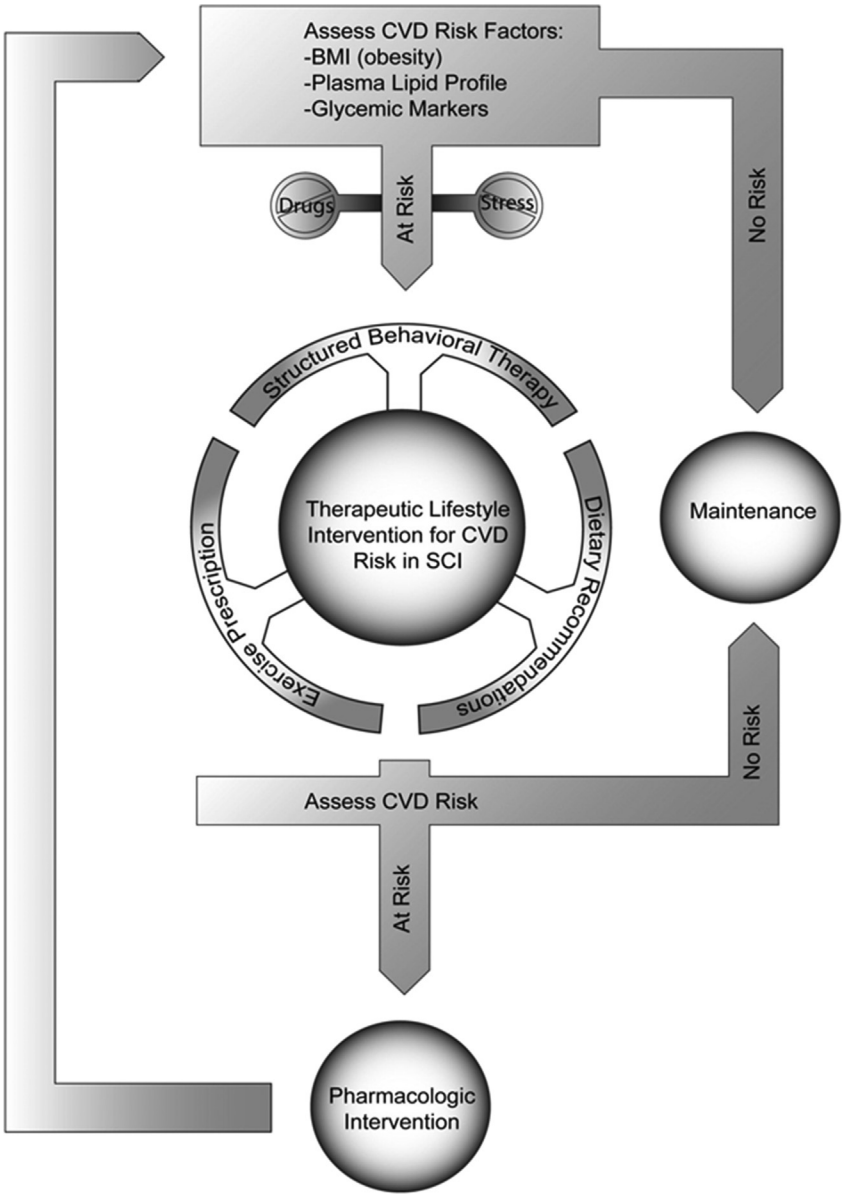


Fig. 1. Clinical pathway outlining the treatment decision-making for reducing cardiometabolic disease in SCI.

Dietary Component of TLI

Based on information from United States Department of Agriculture (USDA) Dietary Guidelines for Americans 2010,[19] adapted for SCI where applicable.

Key points

- Energy intake has to be balanced with output to avoid or reduce obesity and prevent or improve CVD risk.
- Diet recommendations for persons with SCI should follow general guidelines, including increasing whole grain, fruit, and vegetable intake, while reducing salt, simple sugar, saturated fat, and cholesterol intake.
- Specific evidence for persons with SCI is sparse and diet recommendations should follow general guidelines except for BMI targets and energy requirement estimates.

Diet Considerations—Energy Balance, Body Composition, and Malnutrition

Weight maintenance or weight loss is the primary goal of most diet interventions aimed at preventing and reducing obesity and CMS risk. Even modest amounts of body weight reduction can result in marked health benefits.[20,21] Energy (caloric) intake and output are the primary factors determining changes in weight and need to be balanced according to the desired goal (ie, if one desires weight loss one needs to achieve a negative balance [energy intake<energy output]). More specifically, body fat reduction while maintaining (or increasing) lean mass (ie, muscle) should be targeted in an effort to improve body composition. This goal is of particular relevance to the upper extremities in persons with SCI because upper extremity function is crucial for daily activities, pain, and independence.[22–24] Weight loss achieved by reducing caloric intake usually results in 14% to 24% loss in lean tissue mass[25,26] and should therefore be accompanied by an exercise regimen to avoid such losses[27] (see exercise section). In addition to energy balance, dietary interventions should also consider specific nutrition needs to avoid malnutrition (overconsumption and underconsumption of nutrients) and promote optimal health. These key concepts and considerations are explained in detail in discussion below and summarized in **Box 1**.

Assessing energy balance

To set caloric targets for weight loss or maintenance, current energy intake and output need to be assessed. The most direct way of assessing everyday energy intake is to measure all consumed foods and beverages and calculate caloric values from food labels. However, this may be cumbersome and time-consuming, particularly for persons with impaired hand function.[28,29] More practical may be the use of diet recall or food frequency questionnaires (preferably with instruction from a professional[30]) in combination with nutrition analysis software. Multiple different analysis software packages are available including a free online calculator from the USDA (SuperTracker[31]).

Energy output or total energy expenditure (TEE) comprises basal metabolic rate (BMR), physical activity (PA), and energy expenditure (EE) from the breakdown, digestion, absorption, and excretion of food (summed up as the thermic effect of food, TEF). Most TEE (>80%) is accounted for by the by BMR and PA (see exercise section).[32–34] Laboratory assessments of TEE are difficult and expensive and standard "field" techniques often overestimate TEE in persons with SCI.[34] Better estimates of TEE are achieved with specific questionnaires,[34] such as The Physical Activity Scale for Individuals with Physical Disabilities[35] or the Physical Activity Recall Assessment for People with Spinal Cord Injury.[36]

Box 1
Key concepts and considerations for dietary component of TLI

- Assess energy balance
  - Energy intake
    - Diet analysis
  - TEE
    - BMR/REE
    - PA/exercise
    - TEF
- Create caloric deficit
  - Reduce energy intake
    - Reduce calorie-dense foods
  - Increase EE
    - PA/exercise
    - TEF
- Malnutrition
  - Overconsumption of macronutrients
    - Fats, cholesterol, CHO
  - Underconsumption of micronutrients and fiber
    - Vitamin A, D, E, C, B5, and biotin
- Recommended diets
  - Mediterranean
  - DASH

Creating a caloric deficit

After assessing energy balance, a caloric deficit of 300 kcal or less should be created to elicit weight loss. Ideally, this should be from a combination of reduced caloric intake and increased expenditure, although the latter may be difficult for persons with SCI (see exercise section). To achieve the caloric deficit, people should reduce or eliminate primarily energy-dense food high in components associated with elevated CMS risk, such as saturated fats/trans fats, added/refined sugars, refined grains, and alcohol, as outlined in **Table 2**. Increased EE will largely depend on PA and body composition changes affecting BMR and may be difficult for persons with SCI (see exercise section). Increased TEF may contribute to a small extent. Little is known about specific foods that increase TEF, but generally TEF is higher for protein compared with other macronutrients (ie, carbohydrates and fats)[37,38] and may be positively affected by certain micronutrients (reviewed in Ref.[39]). The latter, however, mostly lacks rigorously controlled evidence[39] and should therefore be met with caution. Contrary to common belief, fiber does not seem to augment TEF[40–43] (unless it contains high amounts of polyphenols[44]) but may increase fecal energy loss.[45,46] Of note, people with SCI may have reduced TEF (12% of TEE vs 15% for able bodied [AB][33]). Although reduction of caloric intake is the key to weight loss, it should not decrease to less than 800 kcal/d and may have to be considerably higher depending on the individual's age, size, body composition, activity level, disease status, and other factors that affect

Table 2
Reduce or eliminate high caloric density foods

Food Component Associated with CVD Risk	Examples
Saturated fat (<7% of TEE)	Animal products (except fish), coconut/palm oil, pizza, pastries, tortillas, chips, fried foods, etc.
Trans fats	Margarines, snack foods, pre-prepared dessert, partially hydrogenated oils, etc.
Added sugars	Soda/sports/energy/fruit/tea drinks, cereals, candy, desserts, etc.
Refined grains	Breads, pizza, pastries, tortillas, chips, pasta, prepared foods (mixed dishes), crackers, cereals, etc.
Alcohol (≤1 drink for women, ≤2 for men)	Beer, wine, spirits, liquors, etc.

metabolism.[47–52] Reference values for age and gender have been published by the USDA but likely overestimate energy needs for persons with SCI because of their lower metabolically active mass and PA levels. Studies directly comparing resting energy expenditure (REE) between AB and persons with SCI report on average 10% lower energy requirements for adults with chronic SCI (although this difference is markedly reduced to only 1.4% when REE is normalized to body weight).[32,33,47,52] Average REE for adults with chronic SCI have been reported to range from 1392 to 1855 kcal/d for men[32,33,47,53–57] and 1042 to 1290 kcal/d for women.[32,53] These values likely better represent caloric needs of persons with SCI than those published for the general population and can be used as initial targets for caloric deficits.

Malnutrition

To maximize health benefits, diet interventions need to extend beyond mere caloric balance boundaries and ensure adequate nutrient intake to avoid deficiencies.[58] In addition, excess consumption of dietary components associated with CMS risk should be reduced or eliminated.[58] Dietary Reference Intakes (DRI) have been published by the USDA.[19] Generally, consumption of macronutrients is adequate or excessive for persons with SCI (particularly for fat and cholesterol intakes) with the exception of fiber.[19,28,30,59–64] Fiber is of particular concern for persons with SCI because their most common lipid abnormality is low HDL and fiber consumption is positively related to HDL levels.[65–68] However, high fiber intake (20–30 g/d) may stimulate undesirable changes in bowel function that differ from the non-disabled population, rendering high fiber diets impractical for persons with SCI.[69–71]

Because of the general eating habits of most Americans, several micronutrients are of concern because the likelihood of deficiency is high.[19] These nutrients include potassium, fiber, calcium, and vitamin D as well as iron and folate (women only).[19] Several other nutrients (**Table 3**) are of particular concern for persons with SCI because they are often underconsumed by this population (reviewed in Refs.[28,72]). In addition, sufficient consumption of biotin and vitamin B5 (pantothenic acid) may also be of concern to persons with SCI,[28] although DRIs have not been published by the USDA Dietary Guidelines.[19]

Correcting nutrient deficiencies/excess

If deficiencies are identified, the diet should be augmented with specific foods high in these nutrients. As mentioned above, macronutrient deficiency is rare (except for fiber) for persons with SCI, although sources of the nutrients need to be considered and

Table 3
Dietary reference intake of nutrients often underconsumed by persons with SCI based on USDA dietary guidelines

	Women			Men		
Nutrient, Unit	**19–30 y**	**31–50 y**	**51+ y**	**19–30 y**	**31–50 y**	**51+ y**
Vitamin A (RAE), mcg	700	700	700	900	900	900
Vitamin D,[a] mcg	15	15	15	15	15	15
Vitamin E (AT), mg	15	15	15	15	15	15
Vitamin C, mg	75	75	75	90	90	90
Biotin,[b] mcg	30	30	30	30	30	30
Vitamin B5,[b] mg	5	5	5	5	5	5

Abbreviations: AT, α-tocopherol; RAE, retinoic acid equivalents; TEI, total energy intake.
[a] Assuming minimal sun exposure.
[b] Values are not from USDA Dietary Guidelines but based on date from Yates et al,[145] 1998.

should be mainly from lean meats and seafood (protein), whole grains (carbohydrates), and unsaturated fatty acids (fats).[19] More likely deficiencies are in certain micronutrients (as indicated above). Foods containing nutrients of particular concern to SCI are listed in **Table 4**.[73–80]

Excess intake of macronutrients is common for persons with SCI[28] and should be reduced ideally through reduction of intake of those foods listed in **Table 2**. In addition, salt intake by persons with SCI generally exceeds recommended levels.[59–61,69] These levels are established for the general population because of the positive relation of salt intake with high blood pressure.[19] However, persons with SCI at T6 and above where sympathetic nervous system (SNS) control is likely compromised[13,14] frequently suffer from hypotension.[15] Therefore, increased salt intake particularly in the morning has been recommended for individuals suffering from hypotension.[81,82] In contrast, person with SCI but uncompromised SNS should reduce their salt intake in line with general guidelines (<2300 or 1500 mg/d based on age, ethnicity and disease status).[19]

Table 4
Foods containing micronutrients with reported deficiencies in SCI

Nutrient	Examples of Nutrient Containing Foods
Vitamin A	Liver, fish oil, broccoli, spinach, romaine, collard, turnip, mustard greens, squash, pumpkin, carrot, sweet potatoes, mango
Vitamin D[a]	Salmon, tuna, and mackerel (small amounts also in beef liver, cheese, egg yolks) Dietary supplement fact sheet: vitamin D
Vitamin E	Nuts, seeds, vegetable oils, spinach, romaine, collard, turnip, and mustard greens
Vitamin C	Citrus fruits, tomatoes, potatoes, red and green peppers, kiwifruit, broccoli, strawberries, brussel sprouts, and cantaloupe
Biotin	Brewer's yeast; cooked eggs, especially egg yolk; sardines; nuts (almonds, peanuts, pecans, walnuts) and nut butters; soybeans; other legumes (beans, black eyed peas); whole grains; cauliflower; bananas; and mushrooms
Vitamin B5	Meat, vegetables, cereal grains, legumes, eggs, and milk

[a] Sun exposure can yield a significant amount of Vitamin D.[146,147]

Recommended diets

Dietary recommendations for persons with SCI are usually in line with those adopted for the general population[19] with exceptions for energy intake and sodium targets, as outlined above. Two contemporary dietary strategies that have been proven to positively affect components of the CMS are Mediterranean-style diets and the dietary approaches to stop hypertension (DASH),[83,84] which are summarized in **Fig. 2**.

Exercise component of TLI

Based on (1) The World Health Organizations' Global Strategy on Diet, Physical Activity, and Health[85]; (2) The US Department of Health and Human Services Physical Activity Guidelines for Americans[86]; (3) The Exercise is Medicine's Health Care Providers' Action Guide[87]; and (4) SCI Action Canada.[88]

Key points

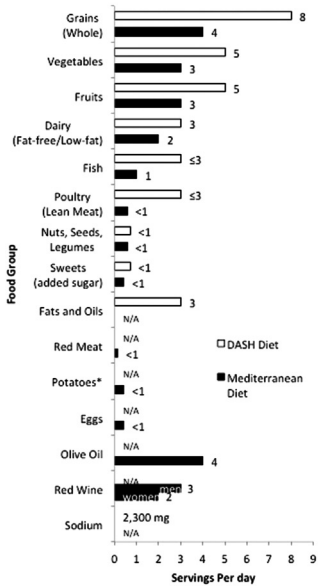
- Exercise absent caloric restriction is unlikely to induce weight loss.
- Exercise recommendations for adults with SCI to improve cardiometabolic risk factors are the same as for adults without disabilities.
- To improve health and wellness, persons with SCI should engage in at least 150 minutes of moderate intensity aerobic exercise each week, perform strength training exercises at least 2 times a week, and stretch at least 2 times a week.

Exercise Considerations—Role in Health and Weight Management

Exercise interventions should be applied with the primary objective of improving metabolic profiles and body composition (not mere weight loss per se). Nevertheless, exercise/PA interventions can augment caloric restriction to accelerate/maintain weight loss. However, as explained in discussion below, for most persons with SCI exercise as a monotherapy will be insufficient to induce weight loss. Although exercise interventions in isolation are unlikely to achieve weight loss for persons with SCI, they are effective for improving strength,[89,90] which in turn support daily independence. Strength gains are also typically associated with an underlying muscle gain and hence positive body composition changes. Over time, increased muscle mass could enhance resting metabolic rate and thus support TEE and weight management.

Exercise and Caloric Balance

Weight loss is achieved through a sustained negative caloric balance as described in the diet component above. Because of lower absolute peak aerobic levels,[91] reduced muscle mass available to expend calories,[92] and autonomic dysfunction[93] (above T6), persons with SCI burn 30% to 50% fewer calories than non-disabled persons during moderate to vigorous exercise intensities.[94] This decreased caloric capacity to burn calories requires increased exercise duration to achieve similar caloric expenditures. Given most non-disabled individuals are challenged to achieve the total weekly recommended PA amounts required to lose weight (60–90 min a day, 5 times a week), it is reasonable to assume the additional time required by persons with SCI (78–135 min a day, 5 times a week) to reach similar caloric expenditures will present an insurmountable obstacle for many. In addition, performing common modes of exercise for SCI such as pushing a wheelchair or using arm ergometry for extended periods of time may also increase the risk for shoulder and wrist overuse injury.



Examples

Food Group	Serving
Whole-wheat breads, pasta, rolls, bagel, cereals, grits, oatmeal, brown rice, popcorn	1 slice bread; 1 oz dry cereal† ½ cup cooked rice, pasta, or cereal†
Broccoli, carrots, collards, green beans, green peas, kale, spinach, squash, tomatoes	1 cup raw leafy vegetable; ½ cup cut-up vegetable; ½ cup vegetable juice
Apples, apricots, bananas, grapes, oranges, mangoes, melons, pineapples, raisins, berries	1 medium fruit; ¼ cup dried fruit; ½ cup frozen/canned fruit; ½ cup juice
Milk or buttermilk; cheese; regular or frozen yogurt	1 cup milk or yogurt 1½ oz cheese
Cod , Salmon, Snapper, Tilapia	1 oz cooked
Select only lean; trim away visible fats; broil, roast, or poach; remove skin from poultry	1 oz cooked
Almonds, filberts, peanuts (butter), walnuts, sunflower seeds, kidney beans, lentils, split peas	⅓ cup or 1½ oz nuts; 2 Tbsp peanut butter; 2 Tbsp or ½ oz seeds; ½ cup cooked legumes
Fruit-flavored gelatin, fruit punch, hard candy, jelly, maple syrup, sorbet and ices, sugar	1 Tbsp sugar; 1 Tbsp jelly or jam; ½ cup sorbet, gelatin dessert; 1 cup lemonade
Soft margarine, vegetable oils (canola, corn, safflower), low-fat mayo, light salad dressing	1 tsp soft margarine; 1 tsp vegetable oil; 1 Tbsp mayonnaise; 2 Tbsp salad dressing
Beef, pork, (all meats from livestock)	1 oz cooked
Potatoes and sweet potatoes	3½ oz
Eggs	1 egg‡
(Extra) Virgin Olive Oil	Use olive oil/rapeseed oil as main added or cooking oil
average strength red wine	4 oz glass
Salt and processed food	≤ 2,300 mg

Fig. 2. Dietary recommendations based on the Mediterranean and DASH diets. *Note*: The Mediterranean-style diets are sometimes considered high in fat content and calories for sedentary populations, although the fats are generally monounsaturated and not the more atherogenic saturated fats. The DASH diet is usually prescribed for hypertension management to a greater degree than fat loss, although high intake of fruits and vegetables in the diet may favor the same weight reduction goals. [a] Potatoes and eggs are included in the vegetable and lean meat groups, respectively, for the DASH diet. [b] Serving sizes vary between $^1/_2$ cup and $1^1/_4$ cups, depending on cereal type. Check the product's nutrition facts label. [c] Eggs are high in cholesterol; therefore, limit egg yolk intake to $\leq$4 per week. (*Data from* NIH National Heart, Lung and Blood Institute. Available at: http://www.nhlbi.nih.gov/health/health-topics/topics/dash/followdash.html; and Brooks G. Mediterranean diet: summary and chart. Available at: http://www.patient.co.uk/health/mediterranean-diet-summary-chart.)

PA Requirements for Weight Loss, Health, and Wellness

The PA levels required for weight loss are much greater than those required to support health and wellness gains (ie, improved cardiometabolic risk factors).[95] Nevertheless, the amount required to support health and wellness in persons with SCI is the same as required for the general population. The World Health Organization (WHO)[85] and the United States Department of Health and Human Services[86] state that guidelines for adults without disabilities can be valid for adults with disabilities. Both organizations note that adjustments can be made as needed to accommodate each individual's exercise capacity, health risks, or limitations. In as much as possible, people with SCI should be encouraged to achieve the minimum targets (**Table 5**).

Exercise Prescription

PA guidelines have been established to be easily comprehensible by the general population but implementation and adherence are greatly enhanced with health care provider guidance. When physician advice is coupled with an exercise plan, patients are 2 times more likely to exercise than those who receive advice but no exercise plan.[96] This increases to 3 times more likely to exercise when physician advice is coupled

Table 5
Target PA levels to improve health and wellness among persons with SCI

Aerobic PA			
Intensity[a]	Moderate		Vigorous
Weekly total[a]	≥150 min Can be accumulated in bouts ≥10 min (eg, 30 min 5 d a wk) (eg, 15 min morning and evening 5 d a wk)	OR	≥75 min Can be accumulated in bouts ≥10 min (eg, 15 min 5 d a wk) (eg, ~11 min every day of the week)
Activity type	Any activity that achieves the above		Any activity that achieves the above
Lay intensity guide[b]	"Somewhat hard," "you can talk but not sing," or is 5 or 6 on a 0 to 10 scale		"Really hard," "you can't say more than a few words without pausing for breath," or is 7 or 8 on a 0 to 10 scale
AND			
Resistance training			
Frequency[a]	≥2 d per wk		
Number of exercises	All major muscle groups[a] (~4–5 upper body exercises). (For shoulder health, be sure to include scapular stabilizer and posterior shoulder muscles.)		
Sets and repetitions[a]	3 sets of 8–12 repetitions (each exercise)		
Weight[b]	Enough to create a feeling of "quite challenged" at the end of each set		
AND			
Upper extremity stretching			
Frequency[c]	2–3 d per wk		
Areas to stretch[c]	Chest and anterior shoulders & perform full range of motion for all upper extremity joints		
When stretching[c]	Apply a gentle, prolonged stretch to each area of tightness		

[a] WHO PA recommendation for adults ages 18–64.
[b] Lay Intensity Guide from SCIAction Canada.
[c] Stretching guideline from Consortium for Spinal Cord Medicine's Upper Extremity Preservation Guideline.

with an exercise plan and regular follow-up queries.[96] Persons with SCI indicate a preference for obtaining PA information from their health care provider.[97] Thus, there is a strong potential that SCI health care providers can increase the PA level of their patients by providing exercise prescriptions.

A Health Care Providers Action Guide from the Exercise is Medicine (EIM) initiative is available online.[87] This initiative is a joint effort by the American College of Sports Medicine (ACSM) and the American Medical Association "to make physical activity and exercise a standard part of a global disease prevention and medical treatment." It is widely supported by professional societies, including the American Academy of Physical Medicine and Rehabilitation (AAPMR), American Physical Therapy Association, American Heart Association (AHA), and the American Osteopathic Association. The Health Care Providers guide is available on the EIM Web site. The guide contains a 4-step PA prescription process, which should be adjusted for SCI as outlined in **Box 2**.

Box 2
Recommended adjustments for patient with SCI to EIM Health Care Providers Action Guide Four-Step Physical Activity Prescription Process

Step

1. If patient is not currently exercising and unwilling to start an exercise program, advise of risks of inactivity (eg, loss of independence, weight gain) and encourage them to exercise.
   i. Recent SCI-specific research indicates loss-framed messages (eg, inactivity risks) result in greater increases in PA than gain-framed messages (eg, PA benefits).[148]
2. Administer Physical Activity Readiness Questionnaire Plus (PAR-Q+), which includes SCI-specific clearance questions/concerns.
3. No SCI-specific adaptation necessary.
4. In addition to aerobic and strength training, recommend a stretching component to help protect the shoulders from overuse. Table 5 presents all components of an exercise prescription.

Specific Considerations for SCI

A "complete" exercise prescription includes aerobic and strength training. In addition, regular flexibility exercise (ie, stretching) should be encouraged to help protect the shoulders from overuse. **Table 5** presents all components of an exercise prescription.

Aerobic exercise considerations

To support health and wellness, the WHO recommends adults aged 18 to 65 perform at least 150 minutes of moderate intensity or 75 minutes of vigorous aerobic PA each week,[85] translating to 30 minutes of moderate intensity or 15 minutes of vigorous intensity activity 5 days a week. Aerobic activity can be accumulated in bouts as short as 10 minutes. For a person with SCI, moderate intensity is described as "somewhat hard," "you can talk but not sing," or is 5 or 6 on a 0 to 10 scale.[88] Vigorous intensity is described as "really hard," "you can't say more than a few words without pausing for breath," or is 7 or 8 on a 0 to 10 scale.[88]

Muscle strengthening considerations

In addition, WHO recommends muscle strengthening activities involving major muscle groups be done 2 or more days a week. For persons with SCI, the specific recommendation is at least 3 sets of 8 to 12 repetitions for each major muscle group 2 times a week.[88] The weight should be enough to create a feeling of "quite challenged" at the end of each set. For most persons with SCI, 4 to 5 different upper extremity exercises should be sufficient to address all upper extremity muscles. It is very important to ensure scapular stabilizers and posterior shoulder muscles are strengthened to protect the shoulder against overuse injuries.

Stretching considerations

In conjunction with strengthening the scapular stabilizers and posterior shoulder muscles, it is critical that persons with SCI stretch their chest (pectoralis muscles) and anterior shoulders (long head of the biceps). The Clinical Practice Guidelines recommend that persons with SCI should stretch 2 to 3 times a week. During each stretching session, they should apply a gentle, prolonged stretch to each area of tightness in the neck, upper trunk, and each arm.[98] In addition, during each stretching session they should perform full range-of-motion exercises for all upper extremity joints.[98]

Referral to a Clinical Exercise Professional

In lieu of or in conjunction with writing an exercise prescription, a health care provider can refer their patient to a clinical exercise professional. Examples of clinical exercise professionals include ACSM-certified clinical exercise specialists and ACSM-registered exercise physiologists. The EIM initiative suggests health care professionals develop a local network of clinical exercise professionals to whom they can refer their patients. By developing a local network, health care providers can ensure local clinical exercise professionals are well versed in the needs, limitations, and health risks of persons with SCI. Alternatively, a local clinical exercise professional can be found by searching the ACSM ProFinder information database.[99]

Managing Shoulder Pain

Upper limb injury is a serious concern for persons undertaking upper extremity exercise, as the prevalence of shoulder pain and injury is 30% to 60% after SCI.[100,101] If shoulder pain is present, circuit training[24] and anterior stretching/posterior strengthening regimens[102,103] are effective treatment options. The exercise prescription can be tailored as needed to minimize pain and injury until more intense exercise is tolerated. This approach is consistent with recommendations for comprehensive upper limb preservation from the Consortium for Spinal Cord Medicine.[98]

Behavioral component of TLI

Adapted from the joint American College of Cardiology (ACC)/AHA task force[19,104] and intended to reflect the behavior modification therapy of the Diabetes Prevention Program (DPP).[105] Modified for SCI where applicable.

Key points

- A comprehensive TLI for CMS risk includes structured behavior modification therapy.
- Key behavioral outcome objectives include
  1. *Education/instruction* on diet and exercise components and role in lowering CVD risk
  2. *Self-monitoring* of body weight, caloric intake, and PA levels, and
  3. Understanding psychosocial barriers and developing *cognitive strategies* to overcome barriers to diet and exercise goals.

Behavioral Modification

Evidence of current CMS prevention guidelines has been set forth by the ACC/AHA and consists of a collective series of documents outlining the assessment, treatment, and management of CMS risk factors, with particular attention to blood cholesterol, overweight, and obesity. Specifically, within the content of the overweight and obesity guidelines, it states that one of the principle components of an *"effective high-intensity…lifestyle intervention"* is the *"use of behavioral strategies to facilitate adherence"* to weight management recommendations. It is asserted that this therapy should provide a *"structured behavioral change program."* As a part of a comprehensive TLI, comprised of diet, PA, and behavior therapy, there is a *"high-to-moderate"* strength of evidence (derived from randomized control trials, meta-analysis, and quality observational studies) for efficacy in facilitating weight loss, when compared with *"usual," "minimal"* care, or no-treatment in the short term (6 months), intermediate (6–12 months), or long term (>1 year).

Key aspects

Several behavioral intervention aspects influence the overall effectiveness of a comprehensive TLI and include frequency and duration of treatment, individual versus group sessions, and onsite versus telephone/e-mail contact. The key behavioral outcome objectives summarized by the ACC/AHA are also outlined extensively in the landmark DPP behavioral program and include: (a) instruction on components of weight management (diet and exercise) and role in lowering CVD risk factors; (b) continuous *"self-monitoring"* with respect to body weight, food intake and composition, and PA level; and (c) cognitive restructuring and developing strategies to overcome psychosocial barriers to program compliance. Data from the DPP report both significant weight loss and a 58% decrease in the incidence of type 2 diabetes mellitus[106] following a structured TLI, consisting of nutrition, exercise, and behavioral weight management. Importantly, the DPP target, greater than or equal to 7% weight loss, was successful in maintaining low-diabetes-rate onset, as reported in a separately designed DPP outcome study (median follow-up of 5.7 years),[107] demonstrating effective long-term lifestyle change and cardiometabolic health benefit.

Several major CVD risk factors,[12,108–116] including overweight/obesity,[59,117–119] are established as pervasive in chronic SCI. Research outlining the impaired psychosocial health, quality of life, and subjective well-being following SCI is extensive (reviewed in Ref.[120]) and, correspondingly, emerging research supports the effectiveness of cognitive behavioral therapy (reviewed in Ref.[121]) in improving health-related quality of life and psychological issues. Although the scope of behavior therapy reviewed was in relation to depression, anxiety, coping, and adjustment post-SCI, it illustrates the potential effectiveness of directed behavior change on secondary complications in SCI.

Recent developments

More recent reports, including the authors' group, have focused on barriers to exercise participation[122,123] and factors influencing dietary status and nutritional habits,[28,29] addressing physical and environmental challenges, and inadequacies in education and psychosocial support, as relevant contributors to these imprudent lifestyle choices, which promote CVD and overweight/obesity risk. As such, a directed cognitive behavioral program as a component of management guidelines for a comprehensive population-specific lifestyle intervention is greatly in need. To our knowledge, there has been one recent uncontrolled study[124] administering dietary and exercise *"advice"* given in 3 *"behavioral change"* consultations over 3 months, and reporting weight loss and reduced BMI. Still, there remain no comprehensive reports of directed intervention trials for obesity and CMS risk factors in SCI. Currently underway, our group is conducting a TLI trial for cardiometabolic disease prevention/treatment in the SCI population. The TLI integrates dietary recommendations, exercise prescription, and structured behavioral therapy, consisting of a 16-session educational program modified from DPP principles to address the specific needs of persons with SCI (**Table 6**). Preliminary data confirm the effectiveness of the TLI in significantly reducing major CVD risk factors, including body weight, BMI, plasma lipid profile, and glycemic markers. These results highlight the potential effectiveness of a TLI for cardiometabolic disease in SCI.

PHARMACOTHERAPEUTIC APPROACHES

Lifestyle intervention incorporating caloric restriction, nutrient modification, and increased daily caloric expenditure usually serve as effective first-line treatments for CMS risks. However, loss of body fat may require unrealistic caloric restriction, and basal and exercise-induced caloric expenditures are decreased in patients with

Table 6
Strategic behavioral modification therapy

	Session	Topic	SCI Considerations	Example of Specific Advice/Information
Diet and exercise principles and goals	1	• Introduction to TLI • Explanation of goals	• Emphasize accelerated CVD risk • Independence	• Physical deconditioning and immobility lead to reduced caloric requirement → Greater likelihood for excess caloric intake • Enhance strength/lose weight to facilitate transfers

	2	• Focus on self-monitoring
		  • Body weight/BMI
		  • Diet (Intake)
		  • Exercise (expenditure)
			• At risk BMI $\geq$22 m/kg^2
			• At risk WC 94 cm
				• Measure body weight weekly
				• Take daily food log
				• Take daily exercise log

	3	• Emphasis on healthy eating
		  • Understanding food labels
		  • Discuss healthy food alternatives
			• Limitations to accessing foods
			• Strategies to make healthier food choices accessible
			• Discuss specific nutritional deficiencies
				• Discuss difficulties getting to and/or shopping at supermarket
				• Have fruits and vegetables in reach at home
				• Whole grains vs refined/processed carbs
				• Vitamins A, D, E, C, B5, biotin, fiber

	4	• Discuss ways to reduce fat intake	• Does caregiver/aide understand healthier food choices	• Discuss calorie dense foods, fat grams • Explain difference/sources of saturated vs unsaturated fats
	5	• Introduction to PA principles in weight control and CMS	• Understanding physiologic limitations in response to exercise • Discuss functional benefit	• Discuss variable responses to exercise (consider level of injury) • Activities of daily living—weight/strength and wheelchair transfer
	6	• Tailoring PA options for maintenance beyond TLI	• Discussing appropriate/feasible aerobic and anaerobic activities • Exploring facilities that provide adaptive support	• Wheelchair sports • In-home exercise (Therabands, Exergaming)[127]
	7	• Discuss principles of energy balance between calories and PA • Discuss principles of health maintenance from exercise	• Discuss how activities of daily living are unique in terms of EE	• Pushing a wheelchair burns less calories than walking a similar distance • Discuss risk of overuse injuries

	8	• Introduce principles of stimulus control
		  • In preventing unhealthy eating
		  • In maintain PA goals
			• Difficulties preparing healthier foods
			• Absence of convenient activities/facilities for disability
				• Do not have unhealthy foods in visible areas
				• Do not eat while involved in other recreation (ie, watching TV)
				• Get schedules of classes that are available so that you can plan ahead

Psychosocial issues and strategies	9	• Present 5-step model of problem solving 1. Define problem in detail 2. Brainstorm options 3. Pick an option to try 4. Make positive action plan 5. Try it and assess	• Preparing healthy foods independently • Access to public activity facilities	• Discuss specific problems that may be inherent to the disability and brainstorm action plans that are appropriate

	10	• Introduce principles of eating/exercising away from home
		  • Planning ahead
		  • Assertion
		  • Stimulus control
		  • Healthy food choices
			• Identifying healthy restaurants and exercise facilities that are adaptive to disability	• If the choice is available, look up and suggest healthier places to eat
				• It is important to be vocal as to your needs to both restaurant employees and those in your social network

	11	• Identifying negative thoughts
		  • "All or nothing"
		  • Excuse
		  • "Should"
		  • "Not as good as"
		  • Give up
		• Coping strategies
		  • Catch yourself
		  • Stop yourself
		  • Replace with positive thought
			• Prevalence of depression	• It is common to compare health-related outcomes to others, either disabled or not, rather than focus on individual progress (ie, a "not as good as" thought)

	12	• Discuss the concept of slips
		  • As a natural part of lifestyle change
		  • Tips to recover behavior modification
			• Individuals experience inherent health complications
			• Need planning/strategies to cope
				• Discuss infection, sores, AD that may interfere with diet/exercise consistency

(*continued on next page*)

Table 6
(*continued*)

Session	Topic	SCI Considerations	Example of Specific Advice/Information

13	• Discuss boredom in TLI program
	  • Dietary
	  • Activity—F.I.T.T.
		• Exercise intensity (as HR)
		• Central vs peripheral RPE
			• For low-level paraplegia, may more closely reflect guidelines than higher-level paraplegia and tetraplegia
			• Central is a more appropriate surrogate for intensity in upper level injury

14	• Discuss strategies for managing social cues
	  • Stressful (negative)
	  • Supportive (positive)
		• Vocalize study and health needs and goals to support group to change the landscape of social environment	• Friends/family members providing energy-dense "comfort" food during rehabilitation and beyond may be counterproductive

15	• Summary of stress management principles
	  • Define/identify stressors
	  • Explore individual signs of stress
	  • Strategies to manage unavoidable stress
	  • Strategies to prevent additional stress
		• Secondary health concerns (AMS risk) are a constant stressor	• Reiterate that intervention represents a modified lifestyle that must be maintained

16	• Focus on enhancing motivation	• Independence (activities of daily living)	• Set specific activity goals (ie, wheelchair transfer) • Using a manual rather than powered wheelchair

Abbreviation: F.I.T.T., frequency intensity time type.

tetraplegia because of diminished active muscle mass and adrenergic dysfunction accompanying injury above the level of spinal sympathetic outflow. In addition, persons with SCI have limited capacity to burn fat during exercise.[125–128] When first-line approaches of diet and exercise fail to modify risk, evidence-based guidelines and current practice standards recommend pharmacotherapy. Very little evidence exists regarding pharmacotherapy for CMS specific to persons with SCI. Approaches developed and tested in the general population serve as general guides, representing default guidelines until SCI-specific evidence is available.

Drug Approaches to Treat Obesity

Three prescription drugs are currently FDA approved for weight loss, although none have been studied in a randomized controlled trial examining persons with SCI. **Table 7** identifies "on-label" drugs for weight loss, approved uses, drug mechanisms, common adverse effects, and "off-label" drugs for weight loss marketed as appetite suppressants ("anorexigenics").

Drug Approaches to Treat Hyperglycemia

The American Diabetes Association (ADA) defines hyperglycemia in nonpregnant adults as glycated hemoglobin (HbA_{1c}) greater than or equal to 6.5% (performed in a laboratory using an National Glycohemoglobin Standardization Program (NGSP)-certified method standardized to the DCCT assay and in the absence of unequivocal hyperglycemia results to be confirmed by repeat testing); or fasting plasma glucose (fasting defined as no caloric intake for 8 hours or more) greater than or equal to 126 mg/dL (7.0 mmol/L); or 2-hour plasma glucose greater than or equal to 200 mg/dL (11.1 mmol/L) during an OGTT (75 g)[2]; or random plasma glucose greater than or equal to 200 mg/dL (11.1 mmol/L) (in persons with symptoms of hyperglycemia or hyperglycemic crisis).[129]

Current ADA treatment recommendations for hyperglycemia[130] are shown in **Box 3**, whereas candidate drugs to treat hyperglycemia after SCI have been reviewed by Goldberg.[131] Eleven classes of oral medication are currently approved to treat hyperglycemia in people with type 2 diabetes. Most of these agents lower HbA_{1c} levels by 0.5% to 2.0%. Depending on pretreatment HbA_{1c} levels, effective treatment may require more than one agent. Recent evidence-based guidelines, including a consensus algorithm for initiation and adjustment of therapy, identified metformin as a preferred first-line agent,[132] as it is less prone to cause hypoglycemia and water retention than other agents, may promote minor weight loss, and is available in generic formulation. Recommended add-ons to achieve A1c targets are glucagon-like peptide-1 receptor agonists (Byetta and Victoza). None of these agents has been systematically tested in persons with SCI, although no available evidence suggests that either benefits or adverse effects would differ from those reported. To the authors' knowledge, no specific data on persons with SCI are currently available; however, preliminary evidence from our laboratory suggests potential benefits of salsalate monotherapy on fasting and postprandial plasma glucose.[133]

Drug Approaches to Treat Dyslipidemia

Five classes of agents are currently used to treat lipid disorders occurring in the general population (**Table 8**). Goldberg has previously described suggested drug choices and nuances for medication selection in persons with SCI.[131] Until recently, need for intervention on an atherogenic lipid profile was determined by the National Cholesterol Education Program Adult Treatment Panel (ATP) III guidelines,[134] which based treatment on whether low-density lipoprotein (LDL) measured in fasting blood plasma

Table 7
Prescription drugs approved for obesity treatment

Drug	Synonyms and Approvals	Drug Description/ Comments	Common Adverse Effects
Orlistat	Sold as Xenical (Rx) and Alli (OTC). Xenical: adults and children ages 12 and older; Alli: adults only 2 y as an adjunct to diet and exercise	A gastrointestinal lipase inhibitor that acts by inhibiting the absorption of dietary fats No evidence suggests that use is suitable in patients with a neurogenic bowel	Stomach pain, gas, diarrhea, and leakage of oily stools Note: Rare cases of hepatotoxicity reported; should not be taken with cyclosporine
Lorcaserin	Sold as Belviq for adult use	Decreases food consumption and promotes satiety by selectively activating 5-HT_{2C} receptors on hypothalamic anorexigenic proopiomelano-cortin neurons	Headaches, dizziness, fatigue, nausea, dry mouth, cough, and constipation. Should not be taken with selective serotonin reuptake inhibitors and monoamine oxidase inhibitor medications WARNINGS for serotonin syndrome or neuroleptic malignant syndrome–like reactions
Phentermine-topiramate	Sold as Qsymia for adult use	Phentermine is a sympathomimetic amine with anorexigenic properties Topiramate is an anticonvulsant promoting appetite suppression and satiety enhancement	Fatigue, paresthesias of hands and feet, dizziness, dysgeusia (particularly with carbonated beverages), insomnia, constipation, and dry mouth MAY LEAD TO BIRTH DEFECTS. DO NOT TAKE IF PREGNANCY MAY OCCUR.
Other appetite suppressants	("off-label" for weight loss): ■ Phentermine ■ Benzphetamine ■ Diethylpropion ■ Phendimetrazine (and other names) Adults (Note: FDA approved up to 12 wk)	Generally classified as sympathomimetic amines and administered as anorectic drugs (schedule IV controlled substances)	Xerostomia, restlessness, nervousness, euphoria, agitation, arrhythmia, tachycardia, hypertension, diarrhea, vomiting, headache, rash, urinary frequency, facial edema, unpleasant taste, urticaria, impotence, changes in libido

Box 3
ADA 2013 Guidelines for type 2 diabetes treatment: hyperglycemia

- Metformin
  - Preferred initial therapy (if tolerated and not contraindicated)
- Consider insulin therapy
  - With or without other agents at outset in newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or A1C
- Add second oral agent, GLP-1 receptor agonist, or insulin
  - If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain A1C target over 3–6 months
- Choice of pharmacologic therapy should be based on a patient-centered approach
- Consider
  - Efficacy
  - Cost
  - Potential side effects
  - Effects on weight
  - Comorbidities
  - Hypoglycemia risk
  - Patient preferences
- Insulin therapy is eventually needed for many patients due to progressive nature of type 2 diabetes

exceeded a criterion target computed from an array of CVD risk factors and prediction equations. Dyson-Hudson and Nash have reviewed testing methods and systematic approaches to ATP III–based treatment decision-making.[135] In general, an intermediate CVD risk stratification was used to define need for treatment, which included

Table 8
Candidate drugs for treating dyslipidemia and expected effects on key elements of the lipid profile

Drug Class	Candidate Drugs	TG %Δ	LDL-C %Δ	HDL-C %Δ
HMG-CoA reductase inhibitors: "Statins"	• Atorvastatin (Lipitor) • Lovastatin (Mevacor) • Pravastatin (Pravacol) • Rasuvastatin (Crestor) • Simvastatin (Zocor)	↓ 10–30	↓ 25–55	↑ 5–15
Cholesterol uptake blocker	• Ezitamibe (Zetia)	↓ 5–15	↓ 15–20	N/A
Bile-acid sequestrates	• Cholestyramine (Questran) • Colesevelam (Welchol) • Colestipol (Colestid)	↑↓ 10–20	↑↓ 20–20	N/A
Niacin releaser	• Niaspan	↓ 10–30	↓ 5–25	↑ 10–35
Fibric acid derivatives	• Atromid (Clofibrate) • Tricor (Fenofibrate) • Lopid (Gemfibrozil)	↓ 30–50	↓ 0–5	↑ 5–20

individuals having Framingham scores of 10% to 20% in the 10-year event risk category, and whose LDL-C levels are greater than 130 mg/dL, or greater than 100 mg/dL in the presence of risk factors including age, hypertension, and/or cigarette smoking or high-sensitivity C-reactive protein greater than 3 μg/L.

More recent guidelines focusing less on lipoprotein targets and more on population risk and need for intervention have been jointly recommended by the AHA and ACC.[136] This change is based on landmark studies showing that improvements in lipoprotein targets do not necessarily lead to better disease outcomes or lower event rates. The guidelines also identify HMG-CoA reductase inhibitors (syn: "statins") as the drug family of choice to anchor both primary and secondary interventions, as they are the most widely studied and have established benefits on disease endpoints and event rates. The guidelines designate 4 different groups for primary and secondary intervention:

1. Individuals who have already had an event and who have CVD (ie, myocardial infarction, unstable angina, stroke, or peripheral vascular disease) become "secondary prevention patients" and are considered at highest risk. They are placed on a high-dose statin (**Table 9**). Measurement of their lipids is not needed, as it is known that prescribing the maximum dose of a statin will maximally reduce their risk for having another event.
2. Individuals with LDL cholesterol level greater than or equal to 190 mg/dL are also considered to be at "very high risk" and are treated with intensive dose statin therapy.
3. Individuals aged 40 to 75 years with diabetes (regardless of type) are considered to be at high risk and are placed on statin therapy. Dosing as moderate intensity or high intensity is based on whether their 10-year risk for an event is greater than or equal to 7.5%. However, they are all put on a statin if they are between the ages of 40 and 75 years.
4. All individuals aged 40 to 75 years who fit within a pooled risk equation identifying a 10-year risk for a CVD event, where statin treatment is indicated if the risk is greater than or equal to 7.5%.

A clinical pathway for treatment decision-making is shown in **Fig. 3**.

Table 9
High-intensity, moderate-intensity, and low-intensity statin therapy (used in the RCTs reviewed by the expert panel)

Intensity	Drug Dose	Effects
Low	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg	Daily dose lowers LDL-C on average, by <30%
Medium	Atorvastatin 10 (20) mg Rosuvastatin (5) 10 mg Simvastatin 20–40 mg Pravastatin 40 (80) mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg	Daily dose lowers LDL-C on average, by approximately 30% to <50%
High	Atorvastatin (40–80 mg) Rosuvastatin 29 (40) mg	Daily dose lowers LDL-C on average by approximately ≥50%

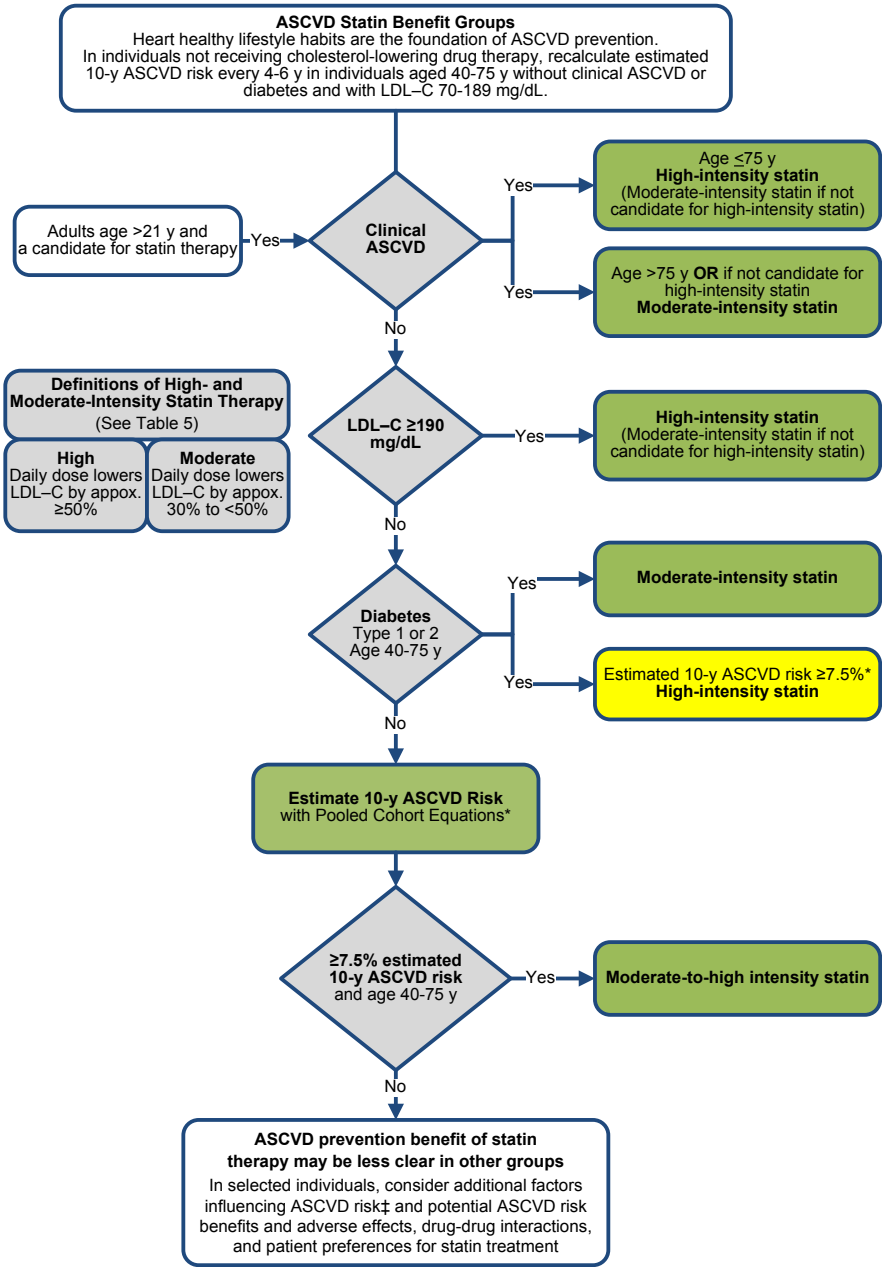


Fig. 3. Clinical pathway for treatment decision-making for dyslipidemia. *, Percent reduction in LDL–C can be used as an indication of response and adherence to therapy, but is not in itself a treatment goal; †, The Pooled Cohort Equations can be used to estimate 10-year ASCVD risk in individuals with and without diabetes. A downloadable spreadsheet enabling estimation of 10-year and lifetime risk for ASCVD and a web-based calculator are available at http://my.americanheart.org/cvriskcalculator and http://www.cardiosource.org/science-and-quality/practice-guidelines-and-quality-standards/2013-prevention-guideline-tools.aspx. (*From* Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Am Coll Cardiol 2013; p.15; with permission.)

Unfortunately, the recent recommendations may have questionable application to persons with SCI, as (1) statins are not the best drugs for correcting the most prominent lipid abnormality after SCI (ie, low HDL-C)[137]; (2) statin-induced myositis[138] may challenge upper extremity function in persons who must use their arms for most daily activities, including wheelchair propulsion; and (3) a clinical trial testing statin safety, tolerance, and effectiveness has never been conducted on persons with SCI.

Nicotinic acid (Niacin) in extended release (ER) formulation represents a tested alternative to use of statins in persons with SCI. Niacin is an older, inexpensive broad-spectrum drug that decreases concentrations of all atherogenic plasma lipids/lipoproteins and is the most effective agent for increasing HDL-C levels.[139] In crystalline (ie, intermediate-release) form, the drug provokes a robust cutaneous flushing, thus compromising patient tolerance when therapeutically dosed. However, an ER formulation of niacin (Niaspan) administered with a prostaglandin antagonist (ie, 325 mg ASA) and gradual dose escalation reduces this discomfort.[140] The therapeutic response to Niacin directly addresses the CMS component risk of low HDL and addresses low HDL as the most common lipid disorder sustained by persons with SCI.[141]

Unlike other candidate drugs for treating SCI-associated dyslipidemia, niacin ER has been subjected to RCT in persons with SCI.[142] Results of 48 weeks of treatment on a dose-escalation schedule showed significant increases in fasting HDL-C levels (24.5%) accompanied by dose-dependent lowering of total cholesterol (TC) and TG (**Fig. 4**) decreases in the global risk predictor ratios of TC/HDL and LDL/HDL, LDL levels, and TC levels. No evidence of sustained hepatotoxicity or hyperglycemia was observed. Treatment-emergent withdrawals (12.9%) accompanied flushing (n = 1), hypotension/presyncope (n = 1), and diarrhea (n = 2), although event rates were lower than those reported for the same agent when treating non-disabled individuals. Although ER niacin use requires diligence in dose escalation, pretreatment with aspirin to suppress the accompanying flush, and abstention from spicy foods, alcohol, and hot showers in the pretreatment period, its use as a monotherapy is safe, tolerated, and effective for most persons with chronic tetraplegia, and it is expected, also paraplegia.

Drug Approaches to Treat Hypertension

Pharmacotherapeutic approaches to hypertension management in the United States have been defined by various sources including the Seventh Report of the Joint

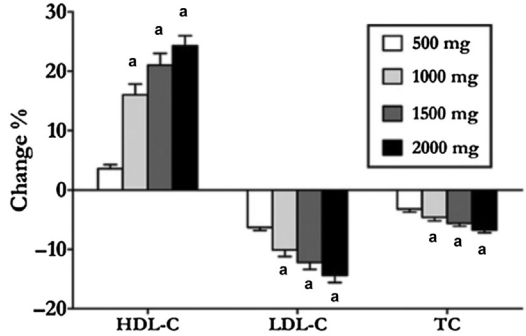


Fig. 4. Results of 48 weeks of Niaspan treatment on a dose-escalation schedule in fasting HDL-C, LDL-C, and TC levels. [a] Significant difference ($P<.05$).

Table 10
Hypertension treatment recommendations and blood pressure targets

Sponsor (Year)	Patient Assessment		Target BP (mm Hg)	Initial Drug Choices
JNC 7 (2003)	No compelling indication	Stage 1 hypertension (SBP 140–159 or DBP 90–99)	<140/90	Thiazide diuretic (for most patients), ACE inhibitor, ARB, β-blocker, CCB, or combination
		Stage 2 hypertension (SBP ≥160 or DBP ≥100)	<140/90	Two-drug combination for most patients (thiazide diuretics plus ACE inhibitor, ARB, β-blocker, or CCB)
	Compelling disease indication	Diabetes mellitus	<130/80	1st: ACE inhibitor or ARB 2nd: thiazide diuretic 3rd: β-blocker, or CCB
AHA and ACC (2007 & 2008)	Primary prevention	Chronic kidney disease	<130/80	1st: ACE inhibitor or ARB
		Framingham risk score <10%	<140/90	ACE inhibitor or ARB, CCB, thiazide diuretic, or combination in needed
		Framingham risk score ≥10%	<130/80	ACE inhibitor (or ARB), CCB, thiazide diuretic, or combination if needed
	High CAD risk	Diabetes mellitus	<130/80	1st: ACE inhibitor or ARB 2nd: thiazide diuretic 3rd: β-blocker, or CCB
		Chronic kidney disease	<130/80	1st: ACE inhibitor or ARB
	CAD	Chronic stable angina Unstable angina Prior acute MI (NSTEMI or STEMI)	<130/80	1st: β-blocker, ACE inhibitor, or ARB 2nd: thiazide diuretic 3rd: CCB
		CAD risk equivalent, carotid artery disease (prior stroke or TIA)	<130/80	1st: ACE inhibitor (or ARB) or thiazide diuretic 2nd: CCB

Abbreviations: ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin-2 receptor blocker; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure,[143] and joint statements from the AHA and American Society of Hypertension (summarized in Ref.[143]). More recent guidelines diverge from earlier recommendations that set grounded hypertension treatment at pressures greater than 140/90 mm Hg. Differences remain between the guideline recommendations with respect to selected pressure targets and first-line drug choices, although common elements include more conservative blood pressure targets (130/80 mm Hg) and drug therapy for primary prevention of hypertension in patients with elevated Framingham risk score. These same targets apply to patients with symptomatic coronary disease, and compelling conditions including diabetes and other comorbidities. Population-specific targets and recommended drugs therapies are shown in **Table 10**.[144] None of these agents have been systematically tested in persons with SCI, although no available evidence suggests that benefits or adverse effects would differ from those currently reported. As mentioned above, any treatment of hypertension needs to be evaluated in light of the nature and level of injury.

SUMMARY

A disconcerting number of people with SCI develop component risks for CMS as they age with their disability. These risks coalesce to comprise a frank diagnosis of the disorder in an alarming number of these individuals. Evaluation and diagnosis of the CMS now fall within the framework of an evidence-based clinical pathway that systematically assesses risk and defines uniform approaches to both individual risk containment and overall disease management.

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